Preliminary Results From a Single Ascending Dose Study in Healthy Volunteers of ACD856, a Positive Modulator of Neurotrophin Trk-Receptors

Boel Nilsson[1] MSc, Matthias Rother[1] MD, PhD, Erik Rein-Hedin[2] MD, Johan Bylund[2] PhD, Magnus M. Halldin[1] PhD, Kristin Önnestam[1] MSc, 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

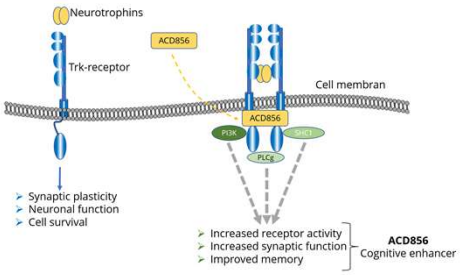
2. CTC Clinical Trial Consultants AB, Dag Hammarskjölds väg 10B, Uppsala, Sweden

Background

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 affects brain anatomy and modulates 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.

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



Objectives

ACD856 is a novel positive allosteric modulator of Trk-receptors in clinical development. The aim of this ongoing study is to assess the safety, tolerability, and pharmacokinetics (PK) of single ascending doses of ACD856.

Methods

56 healthy volunteer subjects were administered ACD856 or placebo as an oral solution in a fasted state in 7 cohorts of stepwise single ascending doses. After each dose, the safety, tolerability, and PK of ACD856 were assessed by an internal Safety Review Committee that decided on escalation of the dose to the next cohort. Additionally, food effect on the PK properties was assessed in 5 subjects participating in a fed cohort.

Fig 2. Study design and dose escalation steps.

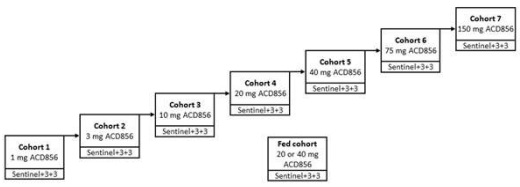


Table 1. Demographics of study subjects and reported adverse events.

Demographics	
Avg. age	36 yrs
Gender - Male - Female	 48 8
Race - White - Asian	 47 9
Avg. BMI	23,6 kg/m²

Reported Adverse Events	
Total # AEs - Mild - Moderate	54 47 6
# AEs with possible causality - Mild - Moderate	25 22 3
Most Common AEs	
Headache	9
Nausea	4

Preliminary Results

Blinded review of the data from 7 cohorts indicate that ACD856 was well tolerated without clinically significant findings in vital signs, physical examination, or urinalysis parameters. Most (47 out of 54) of the reported adverse events (AE) were of mild intensity, a few (6 out of 54) of moderate intensity and none of severe intensity. No serious AEs were reported. Occasional individual abnormal laboratory values were observed, but all except 1 case were assessed as not clinically significant.

The pharmacokinetic data has showed rapid absorption, high bioavailability, terminal half-life of approx. 20 hours and linear dose-dependent exposure. Administration of ACD856 under fed condition resulted in a reduced absorption rate compared to the fasted condition, however the impact of food on the overall bioavailability and the terminal plasma half-life was low.

Fig 3. Plasma concentration curves at the tested dose levels (food cohort not included).

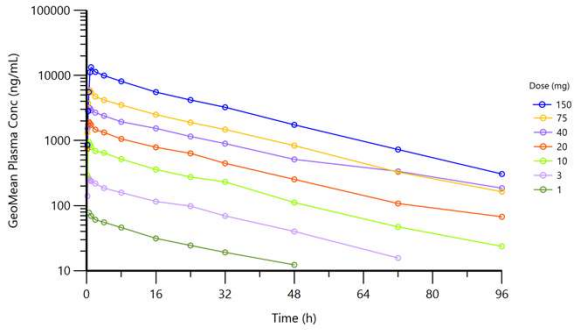


Table 2. Summary of pharmacokinetic parameters (geometric mean and coefficient of variation in percent, except for Tmax median (range)).

Study	Dose (mg)	Adm	n	T_{max} (h)	C_{max} (µg/mL)	AUC_{inf} (h*µg/mL)	CL/F (L/h)	$T_{1/2}$ (h)
µ-dose	0.1	iv	6	NA	NA	0.16 (19.0)	0.63 (19.0)*	19.2 (16.2)
SAD	1	po	6	0.5 (0.5-1.0)	0.08 (15.6)	1.69 (17.6)	0.59 (17.6)	19.8 (11.0)
	3	po	6	0.4 (0.3-2.0)	0.29 (8.3)	6.19 (12.9)	0.48 (12.9)	20.1 (11.3)
	10	po	6	0.5 (0.3-1.0)	0.98 (8.5)	18.9 (13.0)	0.53 (13.0)	18.9 (11.2)
	20	po	6	0.5 (0.3-0.8)	2.03 (15.6)	41.7 (29.7)	0.48 (29.7)	19.7 (18.5)
	40	po	6	0.5 (0.3-0.8)	3.37 (22.8)	82.8 (27.1)	0.48 (27.1)	24.0 (31.4)
	40	po (fed)	<6	6.0 (4.0-8.0)	2.35 (10.9)	83.1 (19.4)	0.48 (19.4)	22.4 (17.7)
	75	po	6	0.5 (0.5-0.8)	6.26 (16.0)	136 (22.0)	0.55 (22.0)	20.7 (22.7)
	150	po	6	1.0 (0.8-1.0)	13.4 (9.4)	289 (10.3)	0.52 (10.3)	19.4 (16.2)

NA, not applicable; *Value represents total body plasma clearance

Conclusion

Preliminary results indicate that ACD856 is safe and well tolerated in man at the tested dose levels and has a suitable pharmacokinetic profile for further clinical development.

In the next step, ACD856 is being evaluated in a multiple ascending dose study.

Hälsovägen 7, 141 57, Huddinge, Sweden
Martin.jonsson@alzecurepharma.com
www.alzecurepharma.com