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

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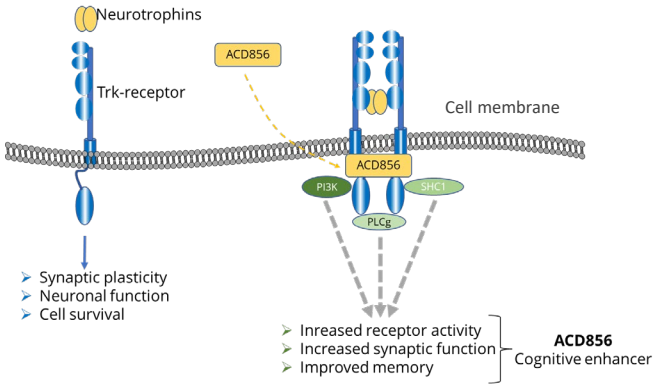

Fig 1. Illustration of ACD856 binding to the Trk-receptor.

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.

Prior to initiating this study, a first clinical study administering an i.v. microdose of ACD856 was completed, providing bioavailability reference data.

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.

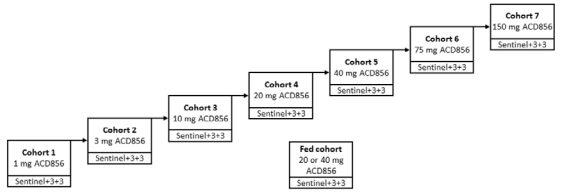

Fig 2. Study design and dose escalation steps completed to date.

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.

Preliminary Results

Blinded review of the data from the first 7 cohorts indicate that ACD856 has so far been well tolerated without clinically significant findings in vital signs, physical examination, or urinalysis parameters. Most of the reported adverse events (AE) were of mild intensity, a few 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 (~100% in comparison with i.v. microdose data), 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.

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

Demographics		Reported Adverse Events	
Avg. age	38 yrs	**Total # AEs**	60
Gender		**- Mild**	54
- Male	48	**- Moderate**	6
- Female	8	**# AEs with possible causality**	27
Race		**- Mild**	24
- White	47	**- Moderate**	3
- Asian	9	**Most Common AEs**	
Avg. BMI	24,1 kg/m^2	**Headache**	11
		Nausea	4

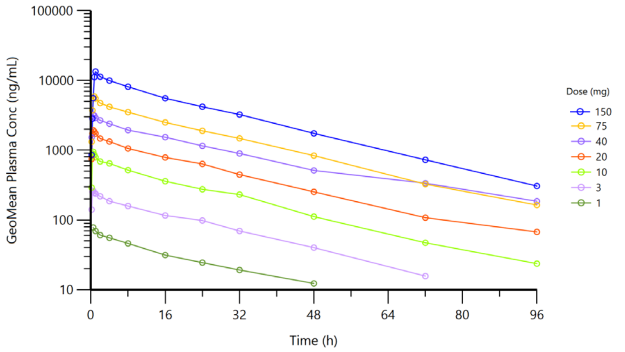

Fig 3. Plasma concentration curves at the tested dose levels (μ-dose and food cohort not included).

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 represent total body plasma clearance

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

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.

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