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

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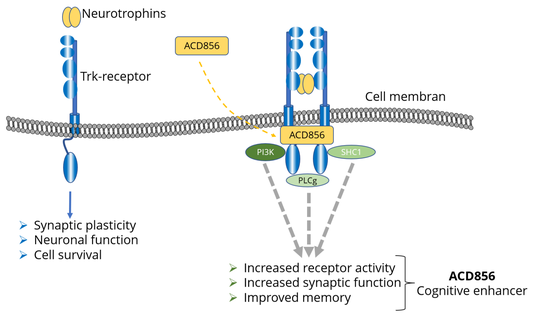
Background

The neurotrophins brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF) 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, and other potential cognitive disorders.

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



Objectives

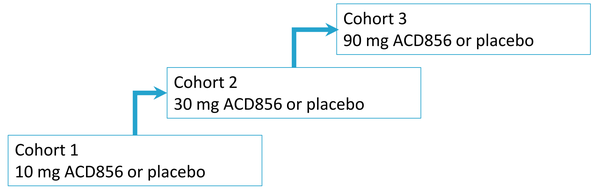
NeuroRestore ACD856 is a novel positive allosteric modulator of Trk-receptors in clinical development for the treatment of Alzheimer's disease and other disorders where cognition is impaired, e.g. Parkinson's disease, TBI and in sleep disorders. The aim of this study was to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of multiple ascending doses of ACD856.

Methods

24 healthy volunteer subjects were administered with ACD856 or placebo as a daily oral solution over 7 days in 3 cohorts of stepwise ascending doses. The cohort dose levels were 10, 30 and 90 mg ACD856 or placebo. In each cohort 6 subjects received active treatment and 2 received placebo. After each dose level, the safety, tolerability, and pharmacokinetics of ACD856 were assessed by an internal Safety Review Committee to decide on the escalation of dose to the next cohort.

On this poster, preliminary safety and PK data is reported. The last subject last dose for the study was completed in May 2022.

Fig 2. Study design and dose escalation steps



Safety Results

Blinded review shows no clinically significant changes from baseline in mean ECG, vital signs, physical examination findings, hematology, coagulation, or urinalysis parameters after receiving the 7 daily doses of ACD856. Occasional individual abnormal laboratory values were observed but all except 3 values for clinical chemistry, elevated lipase or amylase in 2 subjects which returned to normal levels at reassessment, were regarded as not clinically significant.

Most (68 out of 78) of the reported adverse events (AE) were of mild intensity, a few (10 out of 78) of moderate intensity and none of severe intensity. No serious adverse events were reported. Several (16 out of 78) of the reported AEs were associated with the lumbar punction procedure for cerebral spinal fluid (CSF) sampling. It should be noted that safety data is blinded and to date there is no information on which adverse events relate to ACD856 or to placebo treatment.

Pharmacokinetic Results

The blinded pharmacokinetic data confirms the findings from the previously performed single ascending dose (SAD) study, including that ACD856 has a rapid absorption, long half-life of approximately 20 hours, high bioavailability, and a linear dose-dependent exposure. Steady state is reached before administration of the 6th dose. The Cmax at steady state was approximately 1.6-fold higher than the initial dose administration and no time-dependent clearance was observed. No renal elimination of ACD856 was detected.

Measurements of ACD856 in CSF at steady state confirms a relevant CNS exposure. The mean concentrations of ACD856 in CSF increase with dose level; 4.21 ng/ml for the 10 mg cohort, 13.8 ng/ml for the 30 mg cohort, and 100 ng/ml for 90 mg cohort. The observed ratio of measured ACD856 in CSF to unbound average ACD856 levels in plasma was 37% at the lowest dose level and increasing with dose.

Fig 3. Geometric mean plasma concentration curves – linear scale

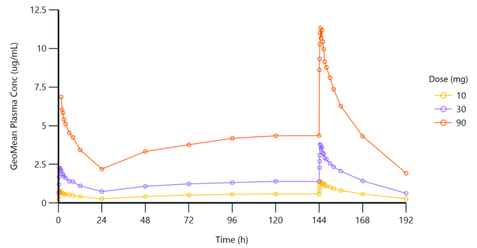


Table 2. Summary of CSF and plasma PK parameters at steady state

MAD Cohort	Dose (mg)	C_{CSF} (ng/mL)	Plasma $C_{avg,\ total}$ (ng/mL)	Plasma $C_{avg,\ unbound}$* (ng/mL)	Ratio C_{CSF} / $C_{avg,\ unbound}$
1	10	4.21 (13.3)	862 (32.1)	10.6 (32.1)	0.37 (27.0)
2	30	13.8 (40.0)	2190 (23.8)	27.0 (23.8)	0.51 (17.0)
3	90	100 (11.2)	6770 (6.9)	83.1 (6.9)	1.20 (17.5)

*$F_{u,\ plasma}$ vale used for estimation of unbound was 1.23%

Table 1. Summary of plasma PK parameters

Study part	Dose (mg)	Dose day	T_{max} (h)	C_{max} (µg/mL)	AUC_{inf} (h*µg/mL)	AUC_{tau} (h*µg/mL)	CL/F (L/h)	$T_{1/2}$ (h)
MAD	10	1	0.5 (0.3-1.5)	0.88 (14.4)	18.3 (27.5)	10.5 (15.5)	0.55 (27.5)	19.5 (22.6)
		7	0.5 (0.3-0.8)	1.46 (27.3)	-	20.7 (32.1)	0.48 (32.1)	23.7 (23.5)
	30	1	0.5 (0.3-1.0)	2.53 (18.0)	49.3 (33.3)	29.1 (16.6)	0.61 (33.3)	18.5 (27.2)
		7	0.6 (0.5-1.5)	3.97 (18.6)	-	52.6 (23.8)	0.57 (23.8)	20.9 (16.1)
	90	1	0.8 (0.3-1.5)	7.49 (3.9)	143 (5.5)	89.9 (4.9)	0.63 (5.5)	16.8 (11.3)
		7	0.5 (0.2-1.5)	12.4 (10.5)	-	162 (6.9)	0.56 (6.9)	19.7 (7.1)

Conclusion

Repeated dosing with NeuroRestore ACD856 was shown to be safe and well tolerated in healthy volunteers at the tested dose levels. Data shows that ACD856 has a suitable pharmacokinetic profile with a linear dose-dependent exposure. Furthermore, the measured ACD856 concentrations in CSF suggests a relevant exposure in the brain.

The results from current study strongly supports further clinical development with ACD856 for the treatment of Alzheimer's disease and other disorders where cognition is impaired.

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