Summary of

Neuroprotective and Disease-Modifying Effects of the Triazinetrione ACD856, a Positive Allosteric Modulator of Trk-Receptors for the Treatment of Cognitive Dysfunction in Alzheimer's Disease

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Neurotrophins are a family of growth factors important for neurons with and as such, they regulate key functions of neuronal cells such as survival, differentiation and the nerve cells capability to communicate with each other via the synapses. Nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) are members of the neurotrophin family, and they bind to cell surface receptors called TrkA, TrkB and TrkC, respectively. We have previously reported on the identification of ACD856 as a positive allosteric modulator (PAM) of Trk-receptors with clear cognitive enhancing effects on induced memory-impairment and natural memory impairment due to old age [1]. These results clearly demonstrate the symptomatic effect of ACD856 on cognitive function.

We have now substantiated the already established symptomatic effects with pre-clinical data demonstrating neuroprotective and neurorestorative effects [2].

First, ACD856 enhanced NGF-induced neurite outgrowth and increased the levels of a synaptic protein important for synaptic function. These findings demonstrate that ACD856 could have a neurorestorative effect in Alzheimer's disease by increasing the number and length of neurites from damaged nerve cells. Also, the effect on synaptic protein, suggest that ACD856 could improve the cellular communication thereby leading to better function in damaged brain areas.

Second, we established that ACD856 was neuroprotective in two different models of neurotoxicity. The first model mimics a pathological situation where the cells have limited access to glucose and pyruvate as energy source. In this model, ACD856 improved cellular integrity and increased the levels both NADH and ATP, two molecules essential for energy-requiring processes in the cells. In the second model, ACD856 was shown to ameliorate amyloid-beta induced neurotoxicity. This model might mimic parts of the toxic events that amyloid beta is responsible for in Alzheimer's disease (AD) and thus, the protective effects of ACD856 in this model might very well lead to a protective effect and a slower disease progression in AD.

Third, ACD856 increased the levels of BDNF itself in both isolated nerve cells and in brain of aged animals which have a natural reduction in the levels of BDNF. The ACD856-induced increment in the levels of BDNF are important since the molecule potentially could have effects that are long lived due to the function and role of BDNF on surrounding tissues.

Fourth, we demonstrated in animals that ACD856 most likely influence neuroplasticity or neuronal networks leading to improved cognition as well as a sustained antidepressant-like effects. In fact, we could demonstrate that the effects of ACD856 sustained for up to one week after administration of the compound.

In summary, the preclinical results demonstrate that ACD856 can improve neuronal integrity, increase synaptic function and plasticity as well as to protect nerve cells from toxic events induced by amyloid beta or low levels of glucose. Combined, these outcomes suggest that ACD856 very well could have a disease modifying ability in AD and together with the positive clinical results from a phase 1 study [3], the results points towards that ACD856 could have supplementary effects to anti-amyloid treatments and function as an adjuvant therapy for the treatment of AD.

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Key references

1. Dahlström, M. et al, Identification of Novel Positive Allosteric Modulators of Neurotrophin Receptors for the Treatment of Cognitive Dysfunction. Cells, 10, 2021
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3. Önnestam, K. et al, Safety, Tolerability, Pharmacokinetics and Quantitative Electroencephalography Assessment of ACD856, a Novel Positive Allosteric Modulator of Trk-Receptors Following Multiple Doses in Healthy Subjects. The journal of prevention of Alzheimer's disease, 2023