In vitro and in vivo profile of AC-0027875 (ACD680), a novel gamma-secretase modulator for the prevention and treatment of Alzheimer's disease

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Objectives

Gamma-secretase modulators (GSMs) are a promising class of compounds for the treatment of early Alzheimer´s disease (AD). Herein we present preclinical data of AC-0027875 (ACD680), a novel GSM in AlzeCure Pharma's Alzstatin® platform.

Background

GSMs exhibit several key features that make them highly suitable as anti-amyloidogenic agents. They reduce the production of amyloidogenic Aβ42, and increase the formation of the shorter peptides Aβ37 and Aβ38, which has been suggested to have some protective properties. These modulators do not block the gamma-secretase activity or change the amount of total Aβ. In fact, GSMs work in the opposite manner to the majority of familiar Alzheimer mutations, i.e. altering the ratio of long vs shorter forms of the Aβ-peptide.

A GSM is suitable as a stand-alone preventive therapy for AD but may also be an attractive option as a maintenace treatment after plaque clearance with Aβ-antibody therapies.

Methods

The in vitro effect of AC-0027875 on the production of various Aβ-peptides was explored in HEK/APPswe cells, mouse and rat primary cortical neurons and human induced pluripotent stem cell-derived cortical neurons using immunoassays specific for Aβ42 and additional gamma-secretase-generated Aβ products. In the in vivo studies, AC-0027875 was administered orally to C57BL/6J mice, and plasma and brain were collected. The compound exposure in plasma and brain tissue was determined by LC-MS/MS. The reduction of soluble Aβ42 in the brain was determined by ELISA.

Results

The GSM AC-0027875 displays high potency in reducing Aβ42 and Aβ40 in HEK/APPswe cells (Fig 1A-B) and an increase in Aβ37 (Fig 1C). It also potently reduces Aβ42 and Aβ40 in both mouse and rat primary cortical neurons (Fig 2,3) as well in human iPSC-derived neurons (Fig 4A). AC-0027875 also increases both Aβ37 and Aβ38 in iPSC-derived neurons (Fig 4B-C) but did not change total Aβ or inhibit Notch processing (Fig 5A-B). AC-0027875 is also highly efficacious *in vivo*, producing a potent lowering of Aβ42 levels over time in a time-response study in mice (Fig 6A). AC-0027875 has a rapid oral absorption and a good exposure as well as an excellent brain exposure (Fig 6B) indicating a suitable profile for further development.

Conclusion

The newly developed GSM AC-0027875 is a promising candidate for further development for the prevention and treatment of Alzheimer´s disease.

Fig 1. Aβ profile of AC-0027875 in HEK APPswe cells

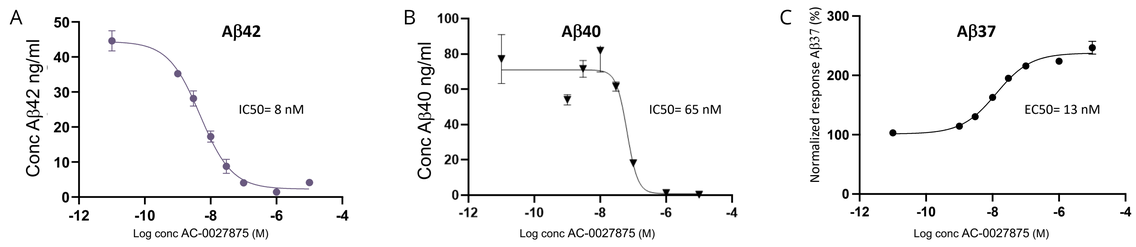

Fig 1. Effect of AC-0027875 on Aβ42 (A), Aβ40 (B) and Aβ37 (C) in HEK APPswe cells. The amounts of Aβ42, Aβ40 and Aβ37 formed were analyzed using ELISA.

Fig 2. Inhibition of Aβ in mPCN

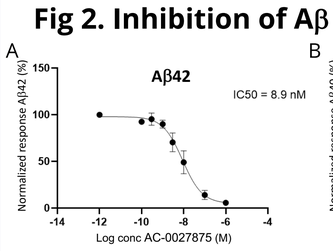

Fig 3. Inhibition of Aβ in rPCN

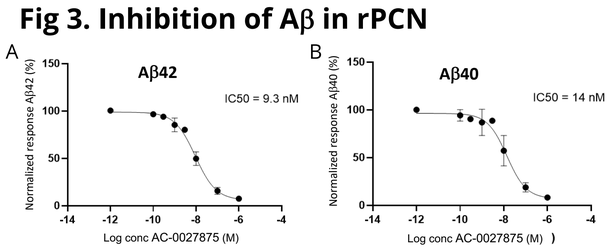

Fig.2, 3. Effect of AC-0027875 on inhibition of Aβ42 (A) and Aβ40 (B) in mouse primary cortical neurons (mPCN, Fig 2) and rat cortical neurons (rPCN, Fig 3). Analysis of Aβ was performed using ELISA.

Fig 4. Aβ profile of AC-0027875 in human induced pluripotent stem cell-derived cortical neurons (iPSC)

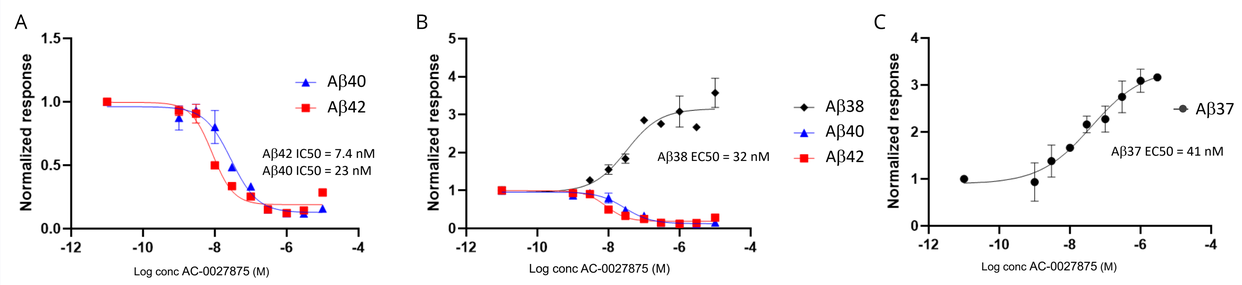

Fig 4. Effect of AC-0027875 on different Aβ species in human induced pluripotent stem cell-derived cortical neurons (iPSC). Aβ38,40,42 analyzed using mesoscale and Aβ37 using ELISA.

Fig 5. Effect of AC-0027875 on total Aβ and on Notch signaling

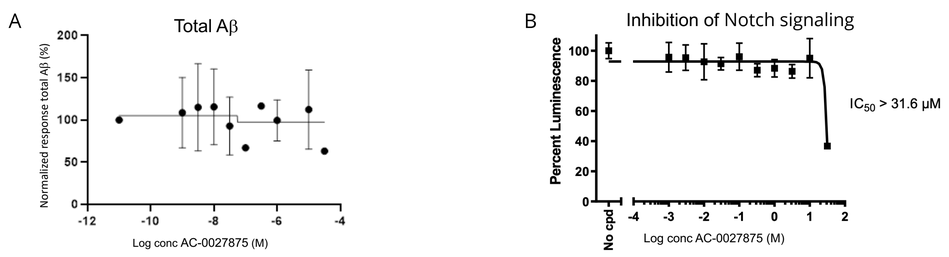

Fig 5. Effect of AC-0027875 on total Aβ in HEK APPswe cells (A) and in Notch/CSL HEK293 cells (B).

Fig 6. Time response study in mouse at 60 µmol/kg AC-0027875

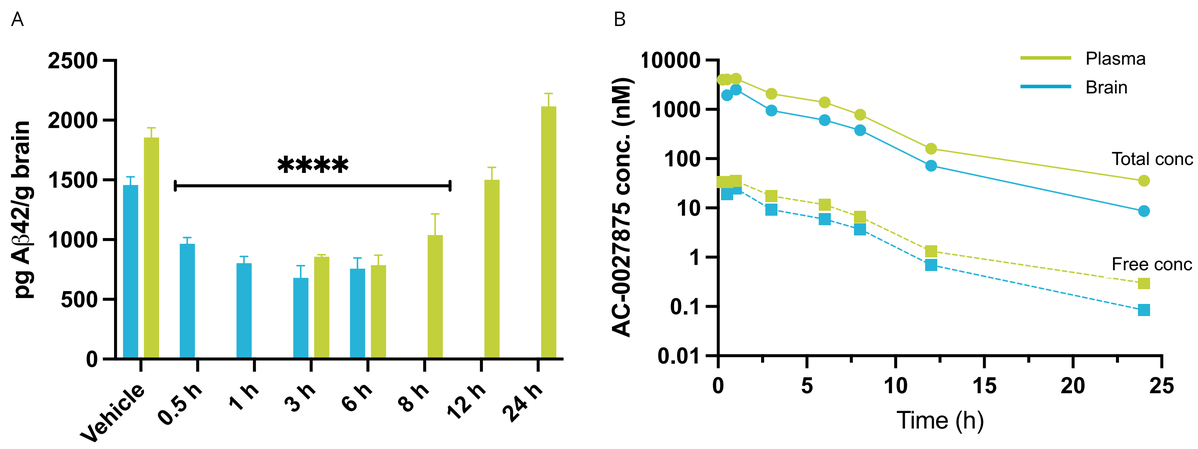

Fig 6. C57BL/6J mice were treated with a single oral dose of 60 µmol/kg AC-0027875 and plasma and brains were collected. (A) Brain tissue levels of soluble Aβ42 over time for two different experiments (blue and green). The amount of Aβ42 is significantly reduced in the 0.5 h to 8 h treatment groups as compared to vehicle group (mean ± SD, One-way ANOVA with Dunnett's multiple comparisons test, ****p < 0.0001). (B) Mean total (solid) and free (dashed) plasma (green) and brain (blue) levels of AC-0027875.

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