AC-0027875, a novel gamma-secretase modulator for the treatment of Alzheimer's disease

Maria Backlund[1], Märta Dahlström[1], Veronica Lidell[1], Azita Rasti[1], Pontus Forsell[1], Sanja Juric[1], Magnus M. Halldin[1], **Johan Sandin[1]**, Gunnar Nordvall[1].

1. AlzeCure Pharma AB, Hälsovägen 7, Huddinge, Sweden.

Objectives

The promising profile of gamma-secretase modulators (GSMs) led us to develop GSM compounds for the treatment of early Alzheimer´s disease (AD). Herein we present preclinical data of AC-0027875, a novel GSM in AlzeCure Pharma's Alzstatin platform.

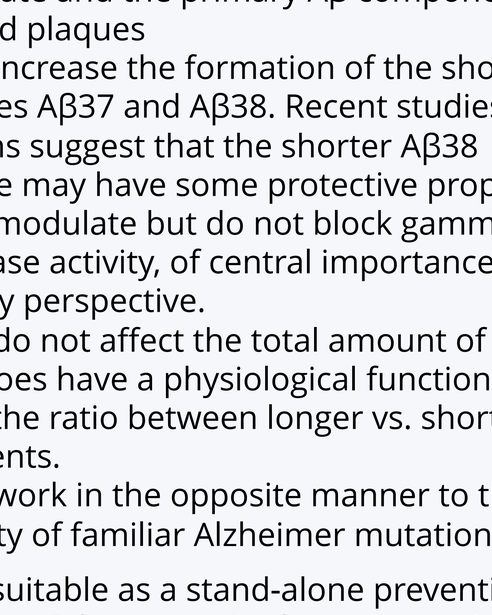
Background

GSMs are a class of anti-amyloidogenic agents that exhibit several key features that make them suitable for the treatment of presymptomatic AD:

1) GSMs target and reduce amyloidogenic Aβ42 production, which is particularly prone to aggregate and the primary Aβ component of amyloid plaques
2) GSMs increase the formation of the shorter peptides Aβ37 and Aβ38. Recent studies in humans suggest that the shorter Aβ38 peptide may have some protective properties.
3) GSMs modulate but do not block gamma-secretase activity, of central importance from a safety perspective.
4) GSMs do not affect the total amount of Aβ, so if Aβ does have a physiological function it only alters the ratio between longer vs. shorter fragments.
5) GSMs work in the opposite manner to the majority of familiar Alzheimer mutations.

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

Fig 1. Illustration of the mechanism of a GSM



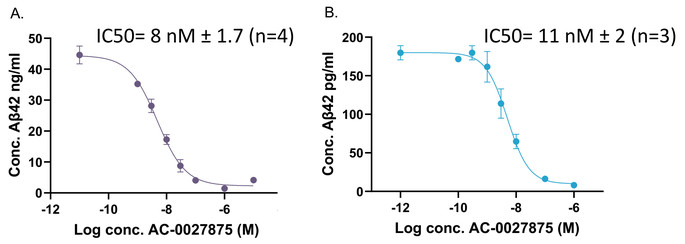
Methods

The effect of AC-0027875 on Aβ42 production was explored both in HEK/APPswe cells and mouse primary cortical neurons (mPCN) and analyzed with an Aβ42 specific ELISA. After oral administration of AC-0027875 to C57BL/6J mice as well as Wistar rats, plasma and brain were collected and 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. The pharmacokinetic profile of AC-0027875 was determined in both mouse and rat.

Results

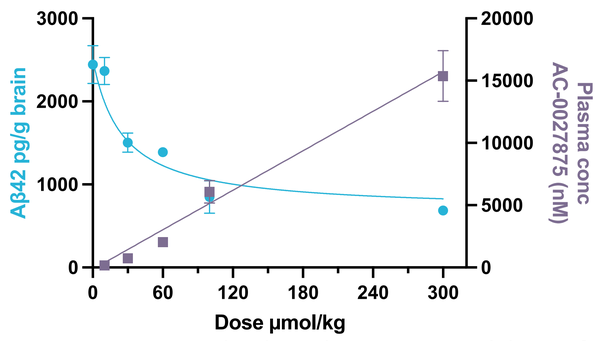
The GSM AC-0027875 displays high potency in HEK/APPswe cells as well as in mouse primary cortical neurons (Fig 2). AC-0027875 is also highly efficacious *in vivo*, lowering Aβ42 levels in both mice (Fig 3) and rats (Fig 4) in dose-response studies. Time-response studies in mice indicate a potent reduction of Aβ42 over time (Fig 5). The PK properties indicate a rapid oral absorption of the drug and good exposure as well as an excellent brain exposure (Fig 5B) indicating a suitable profile for further development.

Fig 2. Human and mouse in vitro potency



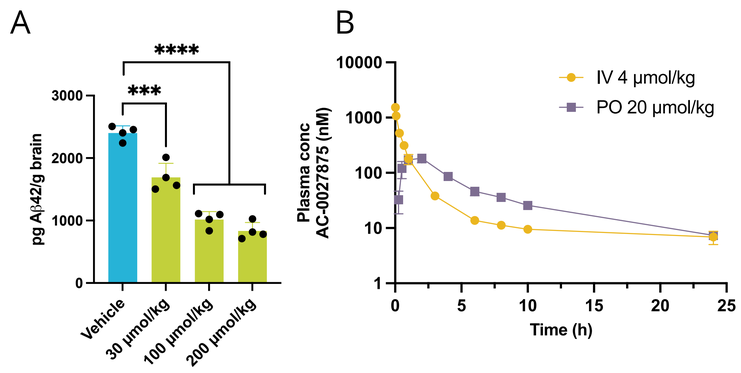
Representative curves showing (A) HEK APP/swe cells and (B) mPCN treated with increasing concentrations of AC-0027875. The amounts of Aβ42 formed were analyzed using ELISA.

Fig 3. Dose response study in mouse



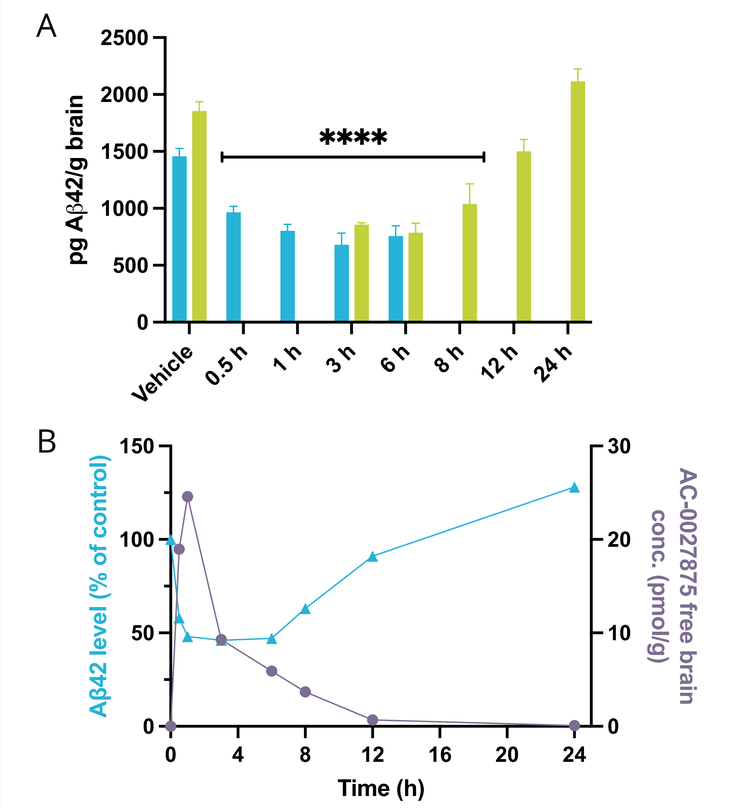
C57BL/6J mice were treated with single increasing oral doses of AC-0027875 and plasma and brain were collected. Blue line shows brain tissue levels of soluble Aβ42, and purple line show total plasma concentration of of AC-0027875 at different doses , respectively, (mean±SD).

Fig 4. Dose response study and PK in rat



(A) Male Wistar rats were treated with single increasing oral doses of AC-0027875 and plasma and brain were collected. Brain tissue levels of soluble Aβ42 at different PO doses of AC-0027875 were analyzed and reduction in Aβ42 is shown as mean ± SD, one-way ANOVA with Dunnett's multiple comparisons test, ***p < 0.001, ****p < 0.0001. (B) PK profile of AC-0027875 at IV dose of 4 µmol/kg and PO dose of 20 µmol/kg (Mean ± SD).

Fig 5. Time response study in mouse at 60 µmol/kg AC-0027875



C57BL/6J mice were treated with a single oral dose of 60 µmol/kg AC-0027875 and plasma and brain 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 brain tissue levels of soluble Aβ42 (blue) and free brain concentration of AC-0027875 (purple) .

Conclusion

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

Martin.jonsson@alzecurepharma.com
www.alzecurepharma.com