EXPERIMENTAL THERAPEUTIC CT1812 DEMONSTRATES TARGET ENGAGEMENT IN A PHASE 1b CLINICAL TRIAL TO MEASURE DISPLACEMENT OF Aβ OLIGOMERS INTO CSF

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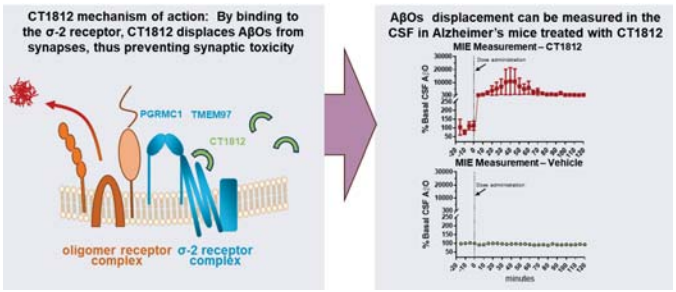
AIMS: A Ph1b clinical trial was conducted to verify target engagement of the sigma-2 receptor (S2R) modulator CT1812 in Alzheimer's disease (AD) patients by measuring drug related increases in Aβ oligomers (AβOs) in CSF.

BACKGROUND: CT1812 is a selective S2R modulator. In preclinical studies it has been shown to displace AβOs from cultured neurons and from cortical tissue slices from postmortem AD patients. In transgenic hAPP/PS1 mice, CT1812 displaces AβOs into the interstitial fluid in the brain and into CSF in the lateral ventricle.



(Izzo, et al, Alz & Dementia 2021)

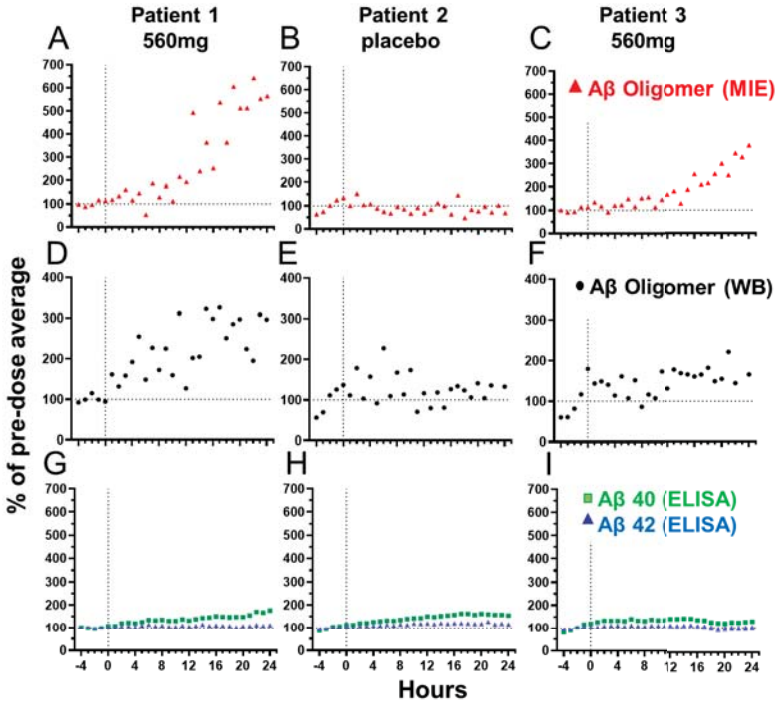
METHODS: A randomized, double-blind, placebo-controlled trial in mild to moderate AD patients (MMSE 18-26, biomarker positive). CSF was drawn from a lumbar catheter hourly over 28 hours, before and after a single p.o. dose of CT1812 (560 mg, two patients) or placebo (one patient).

AβO levels were measured via microimmunoelectrode (MIE) with oligomeric Aβ selective antibody (A11) and by native western blots (WB), Aβ40 & Aβ42 monomer levels were measured via ELISA. All Aβ measurements were normalized to the average of pre-dose levels. CT1812 concentrations were measured by LC/MSMS.

Subject	Treatment	Age Yrs	Sex	MMSE baseline	APOE
Patient 1	560 mg	67	F	18	E3/4
Patient 2	placebo	54	M	22	E3/3
Patient 3	560 mg	52	M	20	E2/3

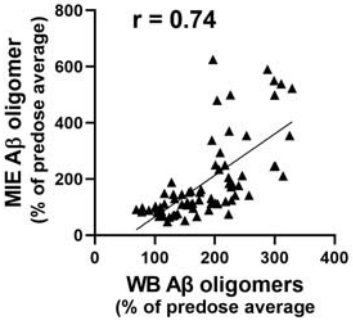
SAFETY: No subjects were withdrawn from the study due to treatment-emergent adverse events. The only serious adverse events were deemed unlikely to be related to study medication but instead due to the lumbar puncture procedure.

CT1812 treatment increases CSF AβOs, but not monomers

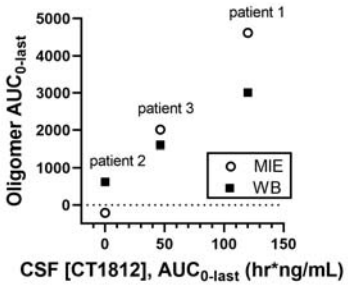


- Patients were dosed at hour 0 (dotted vertical lines).
- CSF concentrations of AβOs (A, B, C) measured by MIE increased >5 fold (Patient 1) and >2.5 fold (Patient 3) with respect to baseline with no apparent change with placebo (Patient 2).
- Similar changes in AβOs (D, E, F) in treated patients were observed on WB
- Aβ40 and Aβ42 (D,E,F) monomers increased <0.5 fold above baseline.

High correlation between AβO assays



AβO in the CSF is related to CT1812 concentration



Left: AβO concentration relative to pre-dose baseline measurements by MIE and by WB were highly correlated (Spearman r = 0.74).
Right: Higher CSF concentration of CT1812 was associated with higher CSF concentration of AβOs as measured by MIE (open circles) or Western blot (closed squares) in the same patients.

CONCLUSION: The results demonstrate the first clinical evidence of target engagement of CT1812 and support that CT1812 can engage S2Rs in brain and selectively mobilize and clear toxic AβOs from AD patient brains.

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