Xanamem™: a novel 11β-HSD1 inhibitor with potential to provide durable symptomatic and disease modifying benefits in Alzheimer's disease.

Ritchie CW[1], Webster SP[1], Cummings J[2], Masters CL[3], Ruffles V[4], Seckl JR[1] & Walker BR[1]

1: University of Edinburgh, 2: Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, 3: Florey Research Institute, Melbourne, 4: Actinogen Medical Ltd, Sydney

Background & rationale

Hypothalamic-pituitary-adrenal axis dysregulation is implicated in AD with cortisol mediating synaptic compromise. 11b-HSD1 regenerates cortisol and amplifies glucocorticoid signaling in key brain regions, notably hippocampus. 11b-HSD1 inhibition in aged mice protects against cognitive dysfunction and reduces amyloid plaque in Tg2576 mice.

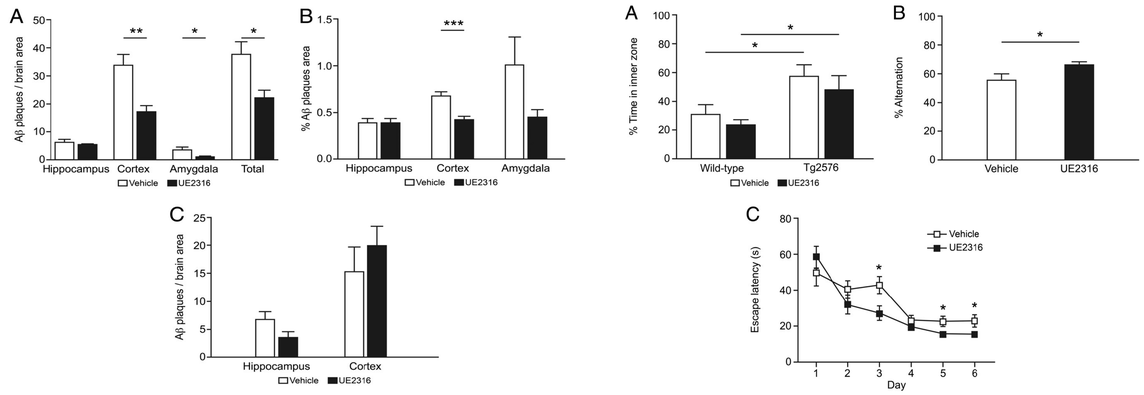
- In preclinical studies, Xanamem™ (a 3,3-disubstituted-(8-aza-bicyclo[3.2.1]oct-8-yl)-[5-(1H-pyrazol-4-yl)-thiophen-3-yl]-methanone) displays high brain penetrance, high potency and selectivity for human 11β-HSD1 when compared to related HSD enzymes and hormone receptors.
- Pre-clinical studies have demonstrated an impact on cognition and amyloid clearance in transgenic mice (Sooy et al., 2015)
- In Phase 1 SAD, MAD and single-dose fed-fasted studies the pharmacodynamic effects of Xanamem™ were monitored by measurement of adrenal steroids in serum, ACTH in plasma, and steroid metabolite ratios in urine.
- A separate study in four healthy volunteers was conducted to determine concentrations of Xanamem™ in CSF. The Phase 2 study design is described.

Conclusions & future plans

A 12-week double-blind, placebo-controlled RCT Phase 2 XanADu study (n=200) is planned for Q4 2016 to assess the efficacy of Xanamem 35mg bd with ADCOMS and ADAS-Cogv14 as co-primary outcomes in mild AD (MMSE 20-26).
20-26).
Xanamem™ is a potent 11β-HSD1 inhibitor being developed for the symptomatic treatment of mild AD. Phase 1 studies have demonstrated that Xanamem™ is safe and well tolerated, gives high pharmacodynamic inhibition and is brain penetrant.

11β-HSD-1 Inhibition & potential positive benefits in Alzheimer's disease

- Impact on transgenic mouse amyloid burden
- Improvements in pre-clinical[1] and clinical[2] cognition
- Successful development of Xanamem™ through Phase 1
- Being developed now in Phase 2 for mild Alzheimer's dementia



Impact of 11β-HSD-1 inhibition on [A] Short Term Plaque Number, [B} Short term Plaque Area and [C] Long Term Plaque Number

Impact of 11β-HSD-1 inhibition on [A] Open field [B} Spontaneous Alteration and [C] Morris Water Maze

PHASE 1 CONCLUSIONS

- Xanamem™ well tolerated, no major safety issues noted.
- After multiple doses plasma drug levels were dose proportional and $t^{1/2}$ ranging from 10-14h.
- ACTH (not plasma cortisol) activated at doses ≥10mg indicating substantial inhibition of extra-adrenal regeneration of cortisol by 11β-HSD1. No dose-dependent changes were observed for testosterone, 4-androstenedione or DHEA-s following multiple doses of Xanamem™.
- The urinary steroid metabolite ratio (THFs/THE) was reduced maximally at doses ≥10mg indicating inhibition of enzyme in the liver.
- Concentrations of Xanamem™ in the CSF were 7.5 to 11.9 % of total plasma levels. The levels of Xanamem™ in the CSF at C_{max} were substantially higher than the cellular IC_{50} for Xanamem™ and compare favourably with CSF data disclosed by AbbVie for the 11β-HSD1 inhibitor ABT-384, where concentrations of ABT-384 in CSF at C_{max} were below its cellular IC_{50}.

References

1. Sooy et al., Cognitive and Disease-Modifying Effects of 11-Hydroxysteroid Dehydrogenase Type 1 Inhibition in Male Tg2576 Mice, a Model of Alzheimer's Disease. *Endocrinology.* 2015 156: 4592–4603
2. Sandeep et al. 11-Hydroxysteroid dehydrogenase inhibition improves cognitive function in healthy elderly men and type 2 diabetics. *Proc Natl Acad Sci USA*. 2004;101:6734–6739.