Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Xanamem (also known as UE2343)

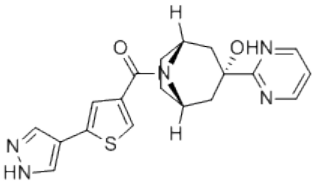
Evidence Summary

Xanamem (as well as a different 11β-HSD1 inhibitor) has failed in Alzheimer's disease clinical trials. 11β-HSD1 inhibitors have been tested in diabetes and obesity with limited success in clinical trials.

Neuroprotective Benefit: Xanamem treatment failed to improve cognitive functions in Alzheimer's patients. Another phase 2a trial of a different 11β-HSD1 inhibitor in Alzheimer's patients also failed to improve cognitive functions.

Aging and related health concerns: No studies have tested Xanamem, but clinical trials of other 11β-HSD1 inhibitors have reported small or inconclusive benefits in type 2 diabetes and obesity.

Safety: Details of safety data and adverse events with Xanamem have only been reported for one of the phase I studies, in which headache, diarrhea, thrombophlebitis, and increased alanine aminotransferase levels were reported.

Availability: in clinical development	**Dose**: The dose tested in Alzheimer's patients was 10 mg once daily (oral). The dose tested in a phase 1 trial in healthy elderly people was 20 mg once daily.	**Chemical formula:** $C_{19}H_{19}N_5O_2S$ **MW**: 381.45  Source: ProbeChem
Half life: 10-19 hours	**BBB**: penetrant	
Clinical trials: The largest study to date is a phase 2 study including 186 Alzheimer's patients.	**Observational studies**: none available	

What is it? Xanamem (also known as UE2343) is under clinical development by Actinogen Medical (Sydney, Australia), an ASX-listed biotechnology company focused on treating cognitive decline in neurological and metabolic diseases. Xanamem is an inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which is an enzyme that converts the stress hormone cortisone (inactive) to cortisol, the active form. Thus, Xanamem blocks the excess production of cortisol, which is seen in many diseases including Cushing's syndrome, obesity, dyslipidemia, hypertension, cognitive decline, and Alzheimer's disease (Gregory et al., 2020). Higher cortisol levels have been associated with impaired cognitive performance in elderly people with type 2 diabetes (Reynolds et al., 2010) and accelerated disease progression in Alzheimer's disease (Cernansky et al., 2006). High 11β-HSD1 activity is observed in obesity and metabolic syndrome; genetic polymorphisms of 11β-HSD1 are associated with diabetes, obesity, and Alzheimer's (Gregory et al., 2020). 11β-HSD1 is abundant in the liver, adipose tissue, and the central nervous system, including the hippocampus. Xanamem is under development for the treatment of Alzheimer's disease, and cognitive impairment associated with schizophrenia and diabetes (Actinogen.com.au).

Neuroprotective Benefit: Xanamem treatment failed to improve cognitive functions in Alzheimer's patients. Another phase 2a trial of a different 11β-HSD1 inhibitor in Alzheimer's patients also failed to improve cognitive functions.

Types of evidence:

- 4 clinical trials testing Xanamem (three phase I studies and one phase 2 study), of which 1 trial had results published in a peer-reviewed journal
- 2 clinical trials testing a different 11β-HSD1 inhibitor (ABT-384)
- Several observational studies examining the relationships between 11β-HSD1 expression, cortisol levels, and dementia risk
- Several laboratory studies testing 11β-HSD1 inhibitors (but not Xanamem, specifically)

Human research to suggest benefits to patients with dementia, or prevention of dementia, prevention of decline, or improved cognitive function:
Xanamem has been studied in three phase 1 studies and one phase 2 study to date, of which results from 1 of the phase 1 studies have been published in a peer-reviewed journal. Results of the others have been discussed in press releases.

In a double-blind randomized controlled phase 1 study in healthy people, single and multiple ascending doses of Xanamem were tested for safety, pharmacokinetics, pharmacodynamics, and blood-brain barrier penetrance (Webster et al., 2017). Xanamem was found to be orally bioavailable, blood-brain barrier penetrant, and showed inhibition of 11β-HSD1 in the liver. Doses tested for the single ascending dose study were 2, 5, 10, 18, 25, and 35 mg. Doses tested for the multiple ascending dose study were 10, 20, and 35 mg, twice daily for 9.5 days. For the study in cerebral spinal fluid (CSF), 35 mg twice daily was given for 4 days and CSF was collected 5 hours post-dose. The mean concentration of Xanamem in the CSF was 69.8 ng/mL (ranging from 41.2 to 99.9 ng/mL) and 7.46 to 11.9% of total plasma levels (and 25-40% of free plasma levels).

In 2016, a phase 2 trial in mild Alzheimer's patients (XanADu trial) was initiated. XanADu was a phase 2 double-blind randomized placebo-controlled trial that tested Xanamem treatment (10 mg daily, oral) for 12 weeks in 186 subjects with mild dementia due to Alzheimer's disease (Actinogen press release; NCT02727699). This trial failed to reach statistically significant differences between Xanamem and placebo in the primary (change in ADAS-Cog version 14; change in ADCOMs) and secondary endpoint measures (RAVLT, CDR-SOB, MMSE, NPI, NTB). However, the 10 mg daily dose of Xanamem appeared safe and pharmacologically active.

Since these results, Actinogen Medical has proposed that higher doses and longer treatment durations are necessary to effectively improve cognition in Alzheimer's disease.

Subsequently, a phase 1 single-blinded randomized placebo-controlled dose escalation study testing higher doses of Xanamem (20 and 30 mg daily) in Healthy Elderly Subjects (XanaHES trial) was carried out (Actinogen press release; NCT03830762). Treatment with Xanamem at the 20 mg daily dose for 12 weeks significantly improved cognition in trial participants compared to those receiving placebo. Based on an exploratory assessment of cognitive function, as measured by the Cogstate Cognitive Test Battery, statistically significant benefits were seen in 2 cognitive domains out of 6: One Back Test of working memory ($p<0.01$ with an effect size of 0.83) and Identification Test of visual attention ($p=0.05$ with an effect size of 0.67). The Detection Test of psychomotor function showed a trend ($p=0.09$). Results also showed that Xanamem treatment significantly reduced serum cortisol levels over the study period.

In contrast, a double-blind randomized controlled trial of Alzheimer's patients reported that treatment with a different 11β-HSD1 inhibitor, ABT-384 (10 or 50 mg/day), for 12 weeks failed to improve cognitive function as measured by ADAS-Cog or any secondary endpoints (Marek et al., 2014). Neither ABT-384 dose demonstrated significant improvement on the primary end point (change from baseline to final score on the 13-item ADAS-Cog) or secondary efficacy end points when compared with placebo. This study was terminated for futility after randomization of 267 participants. The ABT-384 dose that was used in this phase 2 study was associated with complete brain 11β-HSD1 inhibition (Katz et al., 2013), yet the treatment for 12 weeks failed to produce symptomatic improvement in Alzheimer's patients. The authors noted that full inhibition of brain 11β-HSD1 is not a viable approach for treating mild-to-moderate Alzheimer's disease.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
Although higher cortisol levels have been associated with impaired cognitive performance in elderly people (Reynolds et al., 2010) and accelerated disease progression in Alzheimer's disease (Cernansky et al., 2006), findings from laboratory and clinical research with regards to the neuroprotective potential of 11β-HSD1 inhibition have been mixed and inconsistent.

Observational studies: In a case-control observational study of 814 Alzheimer's patients and unrelated control subjects, single-nucleotide polymorphisms in 10 glucocorticoid-related genes were analyzed (Quervain et al., 2014). A rare haplotype in the 5' regulatory region of the HSD11B1 gene encoding 11β-HSD1 was associated with a 6-fold increased risk for sporadic Alzheimer's disease (OR=6.2; 95% CI, 1.4 to

28.4). The rare haplotype of HSD11B1 (rs846911) was significantly overrepresented in AD patients (2.9%) as compared with control subjects (0.5%; p=0.008) and this rare haplotype reduced HSD11B1 transcription. This is counterintuitive and contrast with findings that 11β-HSD1 inhibition could be neuroprotective.

In a brain positron emission tomography (PET) study, 10 lean, 13 overweight, and 5 obese individuals had their brain levels of 11β-HSD1 measured using 11β-HSD1 inhibitor radioligands (11C-AS2471907 or 18F-AS2471907)(Bini et al., 2020). A significant age-associated increase in 11β-HSD1 levels (by 2.7 mL/cm3 per decade) was seen in BMI-corrected mean whole brain distribution volume values. Mean BMI-adjusted whole brain distribution volume value was 6.0 ± 0.6 mL/cm^3 (Mean ± SEM) in individuals 20-30 years old (n = 10), 8.1 ± 0.8 mL/cm^3 in 30-40-year-old people (n = 10), 8.9 ± 1.2 mL/cm^3 in 40-50-year-old people (n = 6), and 15.8 ± 6.8 mL/cm^3 in 50-60-year-old people (n = 2).

Studies in rodents: No published studies have tested Xanamem in rodent models, but other 11β-HSD1 inhibitors have been tested and appear to show neuroprotective and pro-cognitive benefits in some models.

In a mouse model of accelerated aging (SAMP8 mice), treatment with an 11β-HSD1 inhibitor, RL-118 (21 mg/kg/day by oral gavage) for 2 months after being fed a high-fat diet decreased glucocorticoid levels, improved glucose intolerance, restored FGF21 levels, reduced oxidative stress as well as inflammatory markers (IL-1β, IL-4, IL-6, and TNF-α) and microglial activation, and promoted autophagy (Puigoril-Illamola et al., 2020).

In 12-month-old SAMP8 mice, RL-118 treatment (21 mg/kg/day by oral gavage) for 4 weeks increased locomotor activity, improved cognitive performance as measured by object location test, and increased autophagy markers (Beclin1, LC3B, AMPKα, and mTOR)(Puigoril-Illamola et al., 2018). This was accompanied by a decrease in phosphorylated tau species (Ser-396 and Ser-404), modification of amyloid precursor protein towards a non-amyloidogenic pathway, and decreased gene expression of oxidative stress and inflammation markers (e.g., Hmox1, Aldh2, IL-1β, and Ccl3).

Also in 12-month-old SAMP8 mice, treatment with an 11β-HSD1 inhibitor for 4 weeks prevented memory deficits (as measured by the novel object recognition test) and displayed neuroprotective effects (Leiva et al., 2017). Elevations of iNOS and IL-6 were restored with the 11β-HSD1 inhibitor to levels comparable to young SAMP8 mice.

Treatment with an 11β-HSD1 inhibitor, UE2316, improved memory in aged, cognitively-impaired mice and in a mouse model of Alzheimer's disease (Tg2576 mice), while reducing Aβ plaques in the cerebral cortex (Sooy et al., 2015). Chronic treatment of young Tg2576 mice with UE2316 for up to 13 months prevented cognitive decline; however, the treatment did not prevent Aβ plaque formation.

Acute treatment with 11β-HSD1 inhibitors A-801195 (10-30 mg/kg) or A-918446 (3-30 mg/kg) improved memory in rats while increasing phosphorylation of CREB in the cingulate cortex (Mohler et al., 2011).

APOE4 interactions: APOE4 carriers have higher cortisol levels in the cerebral spinal fluid (Peskind et al., 2001); however, interactions with Xanamem in APOE4 carriers have not been reported.

Aging and related health concerns: No studies have tested Xanamem, but clinical trials of other 11β-HSD1 inhibitors have reported small or inconclusive benefits in type 2 diabetes and obesity.

Types of evidence:

- No studies testing Xanamem specifically
- Several clinical trials testing other 11β-HSD1 inhibitors
- Several observational studies examining the relationships between 11β-HSD1 expression, cortisol levels, and metabolic syndrome

Metabolic syndrome: UNKNOWN

No studies have tested the efficacy of Xanamem for metabolic syndrome. In a systematic review of 11β-HSD1 inhibition in human disease, 2 studies examined polymorphisms of 11β-HSD1 in metabolic syndrome, but there were no significant associations between these polymorphisms and biomarkers of metabolic syndrome (Gregory et al., 2020).

Obesity: HIGHER BMI CORRELATED WITH HIGHER 11β-HSD1 EXPRESSION

No studies have tested the efficacy of Xanamem for obesity. However, other 11β-HSD1 inhibitors been tested in overweight and obese patients. Treatment with two 11β-HSD1 inhibitors, MK-0736 (2-7 mg/day) and MK-0916 (6 mg/day), in overweight-to-obese hypertensive patients for up to 24 weeks did not result in a significant improvement in the primary endpoint (placebo-adjusted change in diastolic blood pressure)(Shah et al., 2011). However, treatment with the 7 mg dose of MK-0736 resulted in a placebo-adjusted body weight decrease by 1.4 kg along with decreased LDL and HDL cholesterol.

In a systematic review of 11β-HSD1 inhibition in human disease, 10 studies examined 11β-HSD1 expression in participants who were obese (Gregory et al., 2020). Nine out of the 10 studies showed that 11β-HSD1 expression (measured in abdominal tissue, adipose tissue, or blood) was higher in participants who were obese compared to lean controls, with higher mRNA levels seen in multiple studies.

However this pattern does not appear to be observed in the brain. In a brain positron emission tomography (PET) study, 10 lean, 13 overweight, and 5 obese individuals had their brain levels of 11β-HSD1
measured using 11β-HSD1 inhibitor radioligands (11C-AS2471907 or 18F-AS2471907)(Bini et al., 2020). A correlation emerged between higher BMI with lower levels of the enzyme 11β-HSD1. The age-adjusted mean whole brain distribution volume in lean individuals was the highest in lean individuals (Mean ± SEM; 10.7 ± 0.9 mL/cm^3) and significantly lower in both overweight (7.1 ± 0.9 mL/cm^3; p = 0.01) and obese individuals (5.3 ± 1.3 mL/cm^3; p = 0.01).

This relationship between higher BMI and lower 11β-HSD1 levels was counter to the authors' original hypothesis. However, they speculated that lower 11β-HSD1 levels in the brain with greater BMI may suggest a protective or compensatory mechanism against increased cortisol production and brain exposure. The five individuals with obesity in this study had BMIs ranging from 30 to 32 kg/m^2 (Class I obesity) and the authors hypothesized that more severe obesity (Class II and III) could result in an increase in 11β-HSD1.

Type 2 diabetes: 11β-HSD1 INHIBITION MAY BE BENEFICIAL
No studies have tested the efficacy of Xanamem for type 2 diabetes. However, other 11β-HSD1 inhibitors been tested in diabetes patients. In a double-blind randomized placebo-controlled study of 302 patients with type 2 diabetes, adding an 11β-HSD1 inhibitor, INCB13739, for 12 weeks to ongoing metformin monotherapy resulted in significant reductions in A1C (by -0.6%), fasting plasma glucose (by -24 mg/dl), and HOMA-IR (by -24%) compared with placebo (Rosenstock et al., 2010). In hyperlipidemic patients, total cholesterol, LDL cholesterol, and triglycerides were all significantly decreased. INCB13739 treatment also led to a decrease in body weight relative to placebo.

In a different randomized controlled short-term clinical study in people with type 2 diabetes, treatment with 11β-HSD1 inhibitors (RO5093151/RO-151 and RO5027383/RO-838) showed trends for improvement in HbA1c, though other parameters (HOMA-IR and Matsuda-Index) improved non-significantly (Heise et al., 2014).

Safety: Details of safety data and adverse events with Xanamem have only been reported for one of the phase I studies, in which headache, diarrhea, thrombophlebitis, and increased alanine aminotransferase levels were reported.

Types of evidence:

- 4 clinical trials testing Xanamem (three phase I studies and one phase 2 study), of which 1 trial had results published in a peer-reviewed journal
- 1 double-blind randomized controlled trial testing a different 11β-HSD1 inhibitor (ABT-384)

In a double-blind randomized controlled phase 1 study in healthy people, single (2, 5, 10, 18, 25, and 35 mg) and multiple ascending doses (10, 20, and 35 mg, twice daily for 9.5 days) of Xanamem were tested for safety, pharmacokinetics, pharmacodynamics, and blood-brain barrier penetrance (Webster et al., 2017). Xanamem doses of 2 to 35 mg once daily and 10 to 35 mg twice daily were safe and well tolerated in healthy people. In the single ascending dose study of 48 healthy adults, the number of subjects with more than 1 treatment-emergent adverse events (TEAEs) was 6 in the placebo group and 9 in the Xanamem group, and none of these were associated with any clinically significant changes in vital signs, ECG, biochemistry, hematology, or urinalysis data. In the multiple ascending dose study, there were no serious TEAEs or TEAEs that led to subject withdrawal, and all TEAEs were mild or moderate in intensity. The most common TEAE was headache reported in 7 out of 24 subjects; diarrhea was reported in 2 out of 24 subjects, and thrombophlebitis (a blood clot in a vein causing inflammation and pain) was reported in 3 out of 24 subjects. A study to determine the amount of Xanamem in the CSF was conducted in 4 healthy subjects and all TEAEs were mild to moderate in intensity. Vital signs remained stable during the study. Increased alanine aminotransferase was reported in 1 subject.

Plasma adrenocorticotropic hormone was elevated, as expected as a consequence of systemic enzyme inhibition, at doses of 10 mg and above, but plasma cortisol levels were unchanged (Webster et al., 2017). However, compensatory up-regulation of the hypothalamus-pituitary-axis was noted following multiple doses of 10, 20, and 35 mg Xanamem. DHEA-s and 4-androstenedione were elevated, with effects persisting up to 3 days after the termination of dosing.

In the pharmacokinetic study in dogs, Xanamem showed a clean off-target profile in a diversity screen of 29 enzymes and 72 receptors, including the glucocorticoid and mineralocorticoid receptors (Webster et al., 2017). No significant CYP450 inhibition was observed at isoforms 1A2, 2D6, 2C9 or 3A4 (IC50>50 µM), though moderate inhibition of isoform 2C19 (IC50=1.7 µM) was observed.

In a phase 2 double-blind randomized placebo-controlled trial in 186 mild Alzheimer's patients (XanADu trial), Xanamem treatment (10 mg daily, oral) for 12 weeks was safe and pharmacologically active; however, details of the safety data and adverse events were not provided in the press release (Actinogen press release; NCT02727699).

A subsequent phase 1 single-blinded randomized placebo-controlled dose escalation study testing higher doses of Xanamem (20 and 30 mg daily) in Healthy Elderly Subjects (XanaHES trial) reported that Xanamem at the 20 mg daily dose for 12 weeks exhibited a good safety profile, with no reports of serious adverse events (Actinogen press release; NCT03830762). However, details of the incidences of adverse events were not reported in the press release.

There has been a phase 2 study in Alzheimer's patients testing a different 11β-HSD1 inhibitor. A double-blind randomized controlled trial of Alzheimer's patients reported that treatment with a different 11β-HSD1 inhibitor, ABT-384 (10 or 50 mg/day), for 12 weeks resulted 149 out of 267 subjects experiencing at least one adverse event (55.8%), of whom 82 (30.7%) experienced adverse events that were possibly drug-related (Marek et al., 2014). The overall incidence of treatment emergent adverse events was similar across treatment groups, and no statistically significant differences were observed between the treatment groups and the placebo group in proportions of subjects with possible or probable drug-related, treatment-emergent adverse events. For those receiving ABT-384 (n=135), the most frequent adverse events (≥3.0%) occurring at a greater incidence than placebo included lymphocyte count decrease (n=6; 4.4%), urinary tract infection (n=6; 4.4%), cough (n=6; 4.4%), dizziness (n=5; 3.7%), nasopharyngitis (n=5; 3.7%), and lymphopenia (n=4; 3.0%). Headache was reported by 5.2% of subjects treated with ABT-384 6.1% of subjects in the placebo group, and 6.1% of those taking donepezil. Most adverse events were mild or moderate in severity. While not statistically significant, trends for dose-related increases were seen for nasopharyngitis (0% with placebo, 1.4% with ABT-384 10 mg, and 6.2% with ABT-384 50 mg) and infections (6.1% with placebo, 12.9% with ABT-384 10 mg, and 16.9% with ABT-384 50 mg). With regards to severe adverse events, the ABT-384 10 mg group (n=70) had a higher proportion of subjects (n=6; 8.6%) with at least 1 severe adverse event compared with 0 subjects in the placebo group and 1 subject (1.5%) in the ABT-384 50 mg group. Psychotic disorder was the only severe adverse event that occurred in 2 subjects (both receiving the 10 mg dose). One death due to aspiration pneumonia was reported in the ABT-384 50 mg group, where the onset was 5 days after the last dose and was preceded by general health deterioration and acute renal failure. The death was rated by the investigator as unrelated to study drug. No significant differences were seen between ABT-384 and placebo for vital signs, electrocardiograms, or clinical laboratory tests. However, potentially clinically significant vital sign events included hypertension in 1 subject (ABT-384, 10 mg group), general physical

health deterioration in 1 subject (ABT-384, 10 mg group), and atrial fibrillation in 1 subject (donepezil group). An increase by over 60 milliseconds in Bazett QTc interval was the most frequent potentially clinically significant event in subjects who received ABT-384, as seen in 3 subjects (4.4%) and 1 subject (1.6%) in the ABT-384 10 mg and 50 mg groups, respectively, and 1 subject in the placebo group (1.5%) and 5 subjects in the donepezil group (7.7%). One subject (1.6%) receiving the ABT-384 50 mg dose had an alanine aminotransferase level greater than 3 times the upper limit of normal, which returned to normal without further intervention.

Drug interactions: Drug interactions with Xanamem have not been studied in detail. Based on the pharmacokinetic study, there was moderate inhibition of CYP450 isoform 2C19 (Webster et al., 2017) and thus caution is required when taking other medications that are metabolized by CYP2C19 (e.g., omeprazole, lansoprazole, pantoprazole, citalopgram, amitriptyline, clopidogrel, etc.).

Sources and dosing: Xanamem is under clinical development by Actinogen Medical (Sydney, Australia), an ASX-listed biotechnology company focused on developing treatments for Alzheimer's disease and cognitive decline due to schizophrenia and diabetes. The dose tested in a phase 2 study in Alzheimer's patients was 10 mg once daily, orally, but this dose failed to improve cognitive outcomes (Actinogen press release; NCT02727699). The dose tested in a phase 1 trial in healthy elderly people was 20 mg once daily (Actinogen press release; NCT03830762).

Research underway: There have been 4 completed clinical trials testing Xanamem based on ClinicalTrials.gov, but there are currently no clinical trials that are ongoing.

Patents: Xanamem and related compounds with 11β-HSD1 inhibitor activity are protected in patent applications WO2011033255 and WO2011135276.

Search terms:
Pubmed, Google: Xanamem, UE2343, 11β-HSD1

Websites visited for Xanamem, UE2343:

- Clinicaltrials.gov
- NIH RePORTER (0)
- DrugAge (0)
- Drugs.com (0)
- PubChem (0)
- DrugBank.ca (0)
- Cafepharma (0)
- Pharmapro.com (0)