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

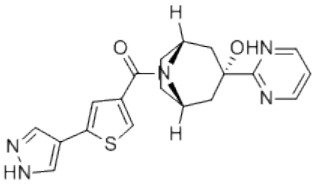
Evidence Summary

Short-term xanamem treatment did not improve cognition in healthy older people or Alzheimer's patients, except in a few cognitive domains. A phase 2b study in Alzheimer's disease is ongoing.

Neuroprotective Benefit: Xanamem treatment did not significantly improve cognitive functions in healthy older people or mild Alzheimer's patients. Based on PET imaging, xanamem shows high 11β-HSD1 occupancy in the brain.

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: In a phase 2 study in Alzheimer's patients, the most common adverse events were headache, dizziness, diarrhea, joint stiffness, and back pain, with incidences comparable to those of placebo. Long-term safety beyond 12 weeks has not been evaluated.

Availability: in clinical development	**Dose**: The dose tested in Alzheimer's patients was 10 mg once daily (oral).	**Chemical formula:** $C_{19}H_{19}N_5O_2S$ **MW**: 381.45  Source: ProbeChem
Half life: 10-14 hours	**BBB**: penetrant	
Clinical trials: The largest study completed 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 impairment 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. 11β-HSD1 is highly expressed in the brain, liver, and adipose tissue (Chapman et al., 2013). Thus, xanamem blocks the excess production of cortisol in these organs. Excess cortisol production 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). Xanamem is under development for the treatment of Alzheimer's disease, and cognitive impairment associated with depression and Fragile X Syndrome (Actinogen.com.au).

Neuroprotective Benefit: Xanamem treatment did not significantly improve cognitive functions in healthy older people or mild Alzheimer's patients. Based on PET imaging, xanamem shows high 11β-HSD1 occupancy in the brain.

Types of evidence:

- 1 double-blind randomized controlled phase 2 study in mild Alzheimer's patients
- 1 double-blind randomized controlled phase 2a study in patients with major depression
- 5 phase I studies
- 1 open-label PET study examining 11β-HSD1 occupancy with xanamem
- 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 five phase 1 studies, two phase 2 studies, and one PET study to date. Results from several of the studies have been published in peer-reviewed journals while results of the others have been discussed in press releases and company webcasts.

In a double-blind randomized controlled phase 1 study in 60 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 xanamem 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 who were clinically diagnosed with mild dementia due to probable Alzheimer's disease (without CSF or PET amyloid confirmation)(Actinogen press release; NCT02727699). This trial did

not 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.

Subsequently, a phase 1 single-blinded randomized placebo-controlled dose escalation study testing higher doses of xanamem (20 and 30 mg daily) in 107 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 ($p=0.09$).

In April 2022, topline results from the phase 1b study (XanaMIA) in healthy people were presented (Actinogen press release; Actinogen webcast slides). In this double-blind, randomized, placebo-controlled phase 1b study, xanamem treatment (5 mg or 10 mg, daily, orally) for 6 weeks in 107 cognitively normal older adults (age 50-80) resulted in improvement in visual attention (Identification Test on Cogstate computerized cognitive test battery) with the 5 mg dose at the end of treatment (Cohen's $d=0.32$; $Z=1.97$; $p<0.05$), but not at Week 4 or at the 4-week follow-up after the treatment, where xanamem and placebo groups had comparable scores (Actinogen press release, 4/27/2022,; Actinogen webcast slides, 4/27/2022). The a priori criterion for effect detection was a Cohen's d of at or above 0.3 in one or more cognitive tests. Although this effect at the 5 mg dose showed a p-value under 0.05, it was not corrected for multiple comparisons. Many cognitive domains were tested, and while the company noted large effect sizes, results were not statistically significant for most domains, including working memory (One Back Test), attention composite, and psychomotor function (Detection Test). For non-attentional cognitive domains, xanamem treatment, both at 5 and 10 mg doses, resulted in numerically worse outcomes for the cognitive composite, delayed recall (CPAR), visual learning (One Card Learning Test), and the IDSST-S (symbol substitution test). Because there were 11 cognitive domains/composites tested, along with 3 time points (Week 4, Week 6, Week 10) and 2 doses (5 and 10 mg), the possibility of false positives is high without statistically controlling for multiple comparisons.

In this phase 1b study, both the 5 mg- and 10 mg- doses showed pharmacodynamic activity evidenced by increased levels of ACTH, a brain hormone that regulates cortisol production in the adrenal gland, by 2.03 and 2.35 times, respectively (Actinogen press release, 4/27/2022,; Actinogen webcast slides, 4/27/2022). These levels were within normal laboratory ranges.

In a prespecified analysis of the phase 2 XanADu trial of mild Alzheimer's patients, blood samples were available and analyzed in 72 patients out of the originally enrolled 185 patients (Taylor et al., 2024). Because this study enrolled patients who were clinically diagnosed with mild Alzheimer's disease without CSF or PET amyloid confirmation, the aim of this prespecified analysis was to identify patients more likely to have Alzheimer's pathology and progressive disease. Plasma ptau181 levels >6.74 pg/mL (median plasma ptau181 level) was used as a cutoff for "high ptau" subjects (n=34) more likely to have progressive Alzheimer's disease. In the placebo group, high ptau patients showed greater clinical worsening over 12 weeks compared to low ptau patients, measured by ADCOMS ($d = 0.55$, $p < 0.001$), CDR-SB ($d = 0.63$, $p < 0.001$), MMSE ($d = 0.52$, $p = 0.12$), and ADAS-Cog14 ($d = 0.53$, $p = 0.19$). In high ptau patients, xanamem treatment (10 mg, daily, orally) for 12 weeks led to a numerical improvement in CDR-SB, a measure of cognition and function, compared to placebo (1.0 in placebo; 0.4 in xanamem; mean difference=0.6; d=0.41), but the difference was not statistically significant (p=0.09). Also in high ptau patients, executive function (measured by the Neurologic Test Battery; NTB) showed numerical improvement with xanamem compared to placebo (0.5 for xanamen, -2.3 for placebo; d=0.26), but the p-value was 0.48. In the same subgroup of 34 high ptau patients, no significant effects of xanamem were seen compared to placebo (with numerically worse scores for xanamem) in a cognitive score (ADAS-Cog14 mean), Alzheimer's composite score (ADCOMS mean), and a neuropsychiatric score (NPI mean).

With regards to plasma biomarkers, xanamem treatment did not significantly alter levels of ptau181, Aβ42/40, NfL, or GFAP (Taylor et al., 2024). Baseline plasma concentrations of ptau181 and Aβ42/40 were low compared to other cohorts with Alzheimer's disease ascertained with amyloid PET imaging, suggesting that the phase 2 XanADu study may have included a heterogenous population not specific to Alzheimer's dementia.

In an open-label imaging study of 17 mild cognitive impairment or Alzheimer's disease patients and 23 cognitively normal people, a PET tracer that specifically binds to 11β-HSD1, [11C]-TARACT (developed by Merck Research Laboratories, PA), was used to assess the degree of 11β-HSD1 occupancy with increasing doses of xanamem (5 mg, 10 mg, 20 mg, or 30 mg daily for 7 days)(Villemagne et al., 2024). With 10 mg of xanamem, 11β-HSD1 occupancy in the mild cognitive impairment/Alzheimer's disease group and cognitively normal groups were 80% and 75% in the neocortex, 69% and 61% in the medial temporal lobe, 80% and 73% in the basal ganglia, and 71% and 66% in the cerebellum, respectively. 11β-HSD1 occupancy with xanamem was high and comparable between cognitively normal and mild cognitive impairment/Alzheimer's groups. Occupancy of 11β-HSD1 by xanamem was similar at doses higher than 10 mg across most regions, exceeding 75% in neocortex. At the 5 mg xanamem dose,

occupancy was approximately 15% lower in the neocortex and 50% lower in the cerebellum. Compared to xanamem dosing in the morning, dosing at night resulted in 11β-HSD1 occupancy that was about 25% lower.

Based on a press release, the phase 2a double-blind randomized controlled trial of 165 patients with depression (XanaCID study) did not meet its primary endpoint of improving the attention composite (composed of 3 Cogstate computerized tests measuring attention and working memory)(PR Newswire, August 12, 2024). Xanamem treatment (10 mg/day) was administered for 6 weeks. Xanamem treatment showed numeric improvement in the secondary endpoint, the MADRS depression score, compared to placebo (difference of 1.5 points; d=0.24); however, the difference between xanamem and placebo groups was not statistically significant (p=0.11). The difference between xanamem and placebo groups was statistically significant 4 weeks after the end of treatment (difference of 2.7 points; d=0.43; p=0.02). In a pre-specified group of 81 patients with less severe depression, xanamem showed significantly greater benefit compared to placebo on the MADRS scores after 6 weeks of treatment (difference of 3.6 points; d=0.88; p=0.02) and 4 weeks after the end of treatment (difference of 3.6 points; d=0.87, p=0.03). In a smaller pre-specified group of 31 patients taking the drug as monotherapy, xanamem treatment showed a trend for improved MADRS scores after 6 weeks of treatment (difference of 4.3 points; d=0.64; p=0.06) but not 4 weeks after the end of treatment. Analyses of other secondary endpoints are ongoing as of August 2024, and include an executive function cognitive composite, a memory function cognitive composite, proportions of responders, and global clinical assessment scores.

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 did not 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). The authors noted that full inhibition of brain 11β-HSD1 may not be 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 as it does not bind to rodent 11β-HSD1, 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 have 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 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: In a phase 2 study in Alzheimer's patients, the most common adverse events were headache, dizziness, diarrhea, joint stiffness, and back pain, with incidences comparable to those of placebo. Long-term safety beyond 12 weeks has not been evaluated.

Types of evidence:

- 1 double-blind randomized controlled phase 2 study in mild Alzheimer's patients
- 5 phase I studies
- 1 open-label PET study examining 11β-HSD1 occupancy with xanamem
- 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.

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) 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, 2019; NCT03830762). However, details of the incidences of adverse events were not reported in the press release or the clinical trial registry.

In a phase 1b study (XanaMIA) of 107 healthy people, xanamem (5 or 10 mg doses) for 6 weeks did not result in treatment-related serious adverse events, and other adverse events were generally equally distributed across the two xanamem and placebo groups (Actinogen slide deck, April 27, 2022).

In the 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 (Actinogen press release, 05/07/2019; NCT02727699). Serious adverse events occurred at comparable rates in xanamem (4/91) and placebo (5/94) groups (NCT02727699). In the xanamem (10 mg daily) group, serious adverse events included 2 cases of pneumonia, 1 case of abnormal vibration test, 1 case of musculoskeletal chest pain, and 1 case of pulmonary cavitation. In the placebo group, serious adverse events included 1 case of acute myocardial infarction, 1 case of influenza, 1 case of fall, 1 case of rib fracture, and 1 case of transient ischemic attack. Other adverse events also occurred in comparable rates in xanamem (33/91) and placebo (32/94) groups. The most common were headache (9.89% in xanamem, 10.64% in placebo), dizziness (8.79% in xanamem, 4.26% in placebo), and diarrhea (6.59% in xanamem, 5.32% in placebo).

The incidence and severity of adverse events were similar in the subgroup of 72 participants whose biomarkers were analyzed as part of the XanADu trial (Taylor et al., 2024). The incidence of treatment-

emergent adverse events (TEAEs) was 83.8% (31/37) in the xanamem group and 57.1% (20/35) in the placebo group. The incidence of TEAEs assessed as related to study drug was 13.5% in the xanamem group and 22.9% in the placebo group. The most commonly observed TEAEs were diarrhea (8.1% in xanamem, 8.6% in placebo), headache (10.8% in xanamem, 5.7% in placebo), arthralgia (joint stiffness; 8.1% in xanamem, 5.7% in placebo), fall (5.4% in xanamem, 8.6% in placebo), back pain (8.1% in xanamem, 2.8% in placebo), and abnormal nerve conduction (2.7% in xanamem, 8.6% in placebo). Serious adverse events were reported in 1 participant in the xanamem group (out of 37; 2.7%) who experienced abnormal vibration test, and 2 participants (out of 35; 5.7%) in the placebo group, who experienced myocardial infarction and transient ischemic attack. None of the serious adverse events were assessed to be related to trial treatment or procedure. There were no withdrawals due to serious adverse events in either group.

In an open-label PET imaging study of 17 mild cognitive impairment or Alzheimer's disease patients and 23 cognitively normal people, xanamem treatment (5 mg, 10 mg, 20 mg, or 30 mg daily) for 7 days did not result in any serious adverse events (Villemagne et al., 2024). Six participants (15%) experienced TEAEs that were possibly related to the study drug, 4 of whom withdrew from the study prior to the second PET scan. Of these 4 subjects, 3 were in the cognitively normal group (one subject receiving 5 mg xanamem who experienced increasing tremors related to pre-existing Parkinson's disease, one subject receiving 20 mg xanamem who experienced fatigue, memory impairment, and depression, and one subject receiving 30 mg xanamem who experienced chest and abdominal pain, tingling in left arm, and dizziness), and one participant was in the mild cognitive impairment/Alzheimer's disease group receiving 30 mg xanamem (hyperactivity, fatigue, hyperventilation, and loss of balance and coordination). With regards to the two participants with TEAEs who remained in the study, one cognitively normal subject who received 30 mg xanamem experienced muscle pain and fatigue, and one mild cognitive impairment/Alzheimer's patient who received 10 mg xanamem experienced nausea and abdominal discomfort. Nervous system disorders and general disorders such as fatigue occurred the most frequently due to xanamem treatment, in 15% and 7.5% of participants, respectively. All TEAEs resolved.

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 with high concentrations of xanamem (Webster et al., 2017). Caution may be 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 development and manufacture by Actinogen Medical (Sydney, Australia), an ASX-listed biotechnology company focused on developing treatments for Alzheimer's disease and cognitive impairment associated with depression and Fragile X Syndrome. The dose tested in a phase 2 study in Alzheimer's patients was 10 mg once daily, orally (Actinogen press release; NCT02727699).

Research underway:

Based on ClinicalTrials.gov, there is one ongoing clinical trial testing xanamem in a phase 2b trial in mild to moderate Alzheimer's disease patients (NCT06125951). This double-blind randomized placebo-controlled study (XanaMIA) is testing the safety, tolerability, and efficacy of xanamem (10 mg daily) for 36 weeks. The primary outcomes are change from baseline in a global cognitive test battery and incidence and severity of treatment-emergent adverse events. Study completion is estimated to be in December 2025.

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)

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