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.

J147

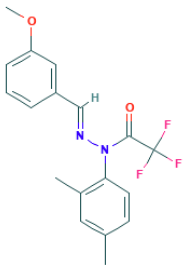
Evidence Summary

Promising preclinical data suggests that J147 may be beneficial in Alzheimer's disease, and the drug targets age-related pathways.

Neuroprotective Benefit: Multiple preclinical studies suggest a benefit in animal models (though all were conducted in one laboratory). No human studies have been conducted.

Aging and related health concerns: J147 targets age-related pathways, though few studies show benefits in age-related diseases.

Safety: No apparent toxicities, but no human data exists.

Availability: Not available, currently in development	**Dose:** J147 was given in food in animal studies at 200 ppm with an estimated daily intake of 10 mg/kg.	**Chemical formula:** $C_{18}H_{17}F_3N_2O_2$; **MW:** 350.34 g/mol  Source: Pubchem
Half life: 1.5 hours (plasma); 2.5 hours (brain)	**BBB:** Yes (in animals)	
Clinical trials: One ongoing	**Observational studies:** None	

What is it?

In an effort to find an Alzheimer's drug that targets the root causes of aging, David Schubert's lab set up phenotypic screens to identify drugs that prevent cell death in cell culture models of the loss of trophic support, oxidative stress, the reduction of energy metabolism (ischemia and glucose starvation models), and amyloid toxicity. They based their molecules on curcumin and cyclohexyl-bisphenol A (CBA), a compound that has neurotrophic activity that curcumin lacks. This led to the identification of CNB-001. Further refinement of the molecule led to J147 (Chen et al, 2011). Later characterization of J147 showed that it partially inhibited ATP synthase (by ~20%), leading to calcium/calmodulin-dependent protein kinase kinase B (CAMKK2)-dependent activation of the AMPK/mTOR pathway (Goldberg et al, 2018).

J147 is under development from Abrexa Pharmaceuticals.

Neuroprotective Benefit: Multiple preclinical studies suggest a benefit in animal models. No human studies have been conducted.

Types of evidence:

- 6 preclinical studies in aged, SAMP8, or Alzheimer's mouse models

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

None

Human research to suggest benefits to patients with dementia:
None

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
Using cell culture models that mimic hallmarks of aging, researchers identified J147 as a neuroprotective molecule that had BDNF-like activities. It increased LTP in hippocampal slices, improved cognition in healthy mice, and improved cognition in a prevention paradigm in an Alzheimer's animal model. J147 also reduced soluble (but not insoluble) Aβ40 and 42 and reduced plaque number (but not size). It also reduced levels of inflammatory proteins (Iba-1 and 5-Lox, but not iNOS), levels of chaperone proteins (HSP 70 and 90) and increased synaptic markers. It increased levels of BDNF and downstream BDNF targets (Chen et al, 2011).

It was also tested in a treatment paradigm in an Alzheimer's model where it improved cognition and anxiety, reduced soluble (but not insoluble) Aβ40 and 42, reduced BACE1 levels, and increased the expression of growth factors (NGF and BDNF) and their downstream targets. It did not change plaque load. In another model of cognitive impairment, J147 improved cognition better than donepezil. It was reported to cross the blood brain barrier, have 28% bioavailability, have negative results on the hERG assay and Ames test, and did not have acute toxicity at 2 g/kg (Prior et al, 2013).

Similar results were seen in SAMP8 mice (a model of accelerated aging) (improved cognition, increased synaptic proteins, reduced Aβ40, reduced ptau, and reduction of some inflammatory markers) (Currais et al, 2015). It improved cognition, increased synaptic markers, and increased neurogenesis in old mice (Prior et al, 2016).

J147 was reported to partially inhibit ATP synthase by ~20%, which led to an increase in signaling through the CAMKK2/AMPK/mTOR pathway. This suggests that partial inhibition of ATP synthase may activate pro-longevity pathways (Goldberg et al, 2018). It also partially inhibits MAO-B and the dopamine transporter, though it is not known if it directly inhibits them (Prior et al, 2013). It was reported to stabilize the hippocampal transcriptome and plasma metabolome drift that occurs with aging. Interestingly, although it partially inhibits ATP synthase, it appears to increase cellular ATP levels (Goldberg et al, 2018).

Studies in human cells reported that an analog, CAD-031, was more neuroprotective and more potent in a human neural progenitor cell assay. CAD-031 also improved cognition and increased neurogenesis in

an Alzheimer's animal model, penetrates the blood brain barrier, has no effect on the hERG assay or Ames test, and has no acute toxicity at 2 g/kg (Prior et al, 2016).

APOE4 interactions:
None

Aging and related health concerns: J147 targets age-related pathways, though few studies show benefits in age-related diseases.

Types of evidence:

- 1 lifespan study in drosophila
- 1 diabetic neuropathy study in mice

J147 increased lifespan in drosophila up to 12.5% and increased ATP in the drosophila head tissue (Goldberg et al, 2018). In a diabetic-induced neuropathy model, treatment of J147 over 20 weeks slightly decreased blood glucose and HbA1c levels, RNA pathways in the CNS related to mTOR signaling, TNF receptor signaling, and type 1 diabetes while increasing AMPK signaling, synaptic signaling, and ephrin receptor signaling. It decreased protein levels of TNFα, GFAP, iNOS, and TSPO. In the periphery it decreased CRP and increased AMPK. It also improved nerve conduction velocity and pain nociception (Daugherty et al, 2018).

Safety: No apparent toxicities, but no human data exists.

Types of evidence:

- 6 preclinical studies

There are no reported toxicities; however, there are no human studies.

Drug interactions:
Unknown, although it acts through the AMPK/mTOR pathway, so it could potentially interact with drugs such as metformin or rapamycin. J147 is also a dopamine reuptake inhibitor and should not be used with dopaminergic drugs.

Sources and dosing:
J147 was given in food in animal studies at 200 ppm with an estimated daily intake of 10 mg/kg.

Research underway:
Abrexa Pharmaceuticals, developing J147, is recruiting for a phase 1 safety study (NCT03838185).

Search terms:
J147 - pubmed