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.

BMS-984923 (ALX-001)

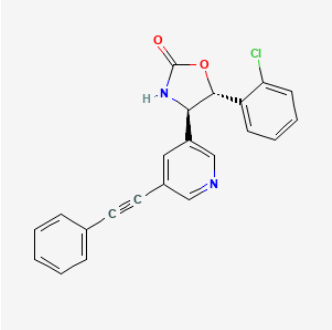
Evidence Summary

BMS-984923 restores cognitive deficits and synaptic loss in mouse models of Alzheimer's disease. Early phase clinical trials are currently ongoing.

Neuroprotective Benefit: Studies in rodent models of Alzheimer's disease have found that BMS-984923 treatment, started well after the emergence of pathologies, restored cognitive deficits and reversed synapse loss. Clinical trials are ongoing.

Aging and related health concerns: BMS-984923 has not been explored for the treatment of age-related diseases beyond neurodegenerative conditions.

Safety: A phase I single dose escalation study in healthy older adults has shown that doses up to 200 mg did not cause any serious adverse events and there were no clinically significant changes in safety assessments. Long-term safety has not been established.

Availability: in clinical development	**Dose**: Not established; clinical trials are ongoing and testing doses of 50, 100, and 150 mg twice daily, orally.	**Chemical formula:** $C_{22}H_{15}ClN_2O_2$ **MW**: 374.8  Source: PubChem
Half-life: not documented for humans	**BBB**: penetrant	
Clinical trials: A phase I single-ascending dose study enrolled 36 healthy older adults.	**Observational studies**: none available	

What is it?

BMS-984923 (also known as ALX-001) is a silent allosteric modulator of the metabotropic glutamate receptor 5 (mGluR5). BMS-984923 blocks the mGluR5 interaction with cell surface cellular prion protein (PrP^c) bound to amyloid beta oligomer (Aβo); however, it does not affect physiological glutamate signaling (Haas et al., 2017). Aβ oligomers binding to PrP^C leads to synaptic dysfunction (Lauren et al., 2009) and the physical interaction between PrP^C and mGluR5 controls the transmission of neurotoxic signals. PrP^C is coupled to mGluR5 through intracellular mediators (Homer1b/c, CaMKII, and proline tyrosine kinase 2 beta [Pyk2])(Haas et al, 2016). mGluR5 is a transmembrane receptor physically linked to the GluN2 subunit of glutamate NMDA receptors (NMDARs) and is localized peri-synaptically at the post-synaptic membrane of glutamatergic neurons. Activation of mGluR5 increases calcium levels inside the cell prompting protein kinase C (PKC) activation (Kumar et al, 2015).

Some evidence suggests that oligomeric Aβ, more than amyloid plaques themselves, are neurotoxic in Alzheimer's disease. For example, individuals with the Osaka mutation (a small group of individuals in Japan) develop dementia without the presence of amyloid plaques. In these patients, increased levels of high-molecular weight amyloid species are seen in their cerebral spinal fluid, presumably oligomeric Aβ. Preclinical studies have implicated oligomeric Aβ in the development of tau pathology, impairment of axonal transport, synaptic degeneration, oxidative stress, insulin resistance, and neuroinflammation (Cline et al, 2018).

BMS-984923 was originally identified by Bristol Myers Squibb, and Allyx Therapeutics, Inc. obtained an exclusive worldwide license to develop it for the treatment of neurodegenerative diseases. Clinical trials in Alzheimer's disease and Parkinson's disease are ongoing.

Neuroprotective Benefit: Studies in rodent models of Alzheimer's disease have found that BMS-984923 treatment, started well after the emergence of pathologies, restored cognitive deficits and reversed synapse loss. Clinical trials are ongoing.

Types of evidence:

- Several PET imaging studies investigating mGluR5 distribution and levels
- Several postmortem tissue studies of Aβ oligomers and PrP^C
- Numerous laboratory studies

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

No studies have tested whether BMS-984923 prevents dementia or age-related cognitive decline in humans.

Human research to suggest benefits to patients with dementia:

No studies of BMS-984923 have been completed in patients with dementia, as of June 2024. A double-blind randomized placebo-controlled phase 1b study is ongoing and is testing multiple ascending doses of BMS-984923 (50, 100, and 150 mg, twice daily, orally) for up to 28 days in healthy volunteers and in people with Alzheimer's disease to assess its safety and tolerability (NCT05804383).

In a PET imaging study of 35 people (19 Alzheimer's patients and 16 normal controls), mGluR5 availability (measured by the mGluR5 tracer [18F]PSS232) was significantly reduced in the hippocampus and parahippocampal gyrus of Alzheimer's disease patients compared to normal controls (Wang et al., 2024). Global amyloid deposition (measured by [18F]Florbetapir PET) was positively associated with mGluR5 availability in Alzheimer's patients, but inversely associated in normal controls. The availability of mGluR5 in the hippocampus and parahippocampal gyrus was inversely correlated with plasma p-tau181 and plasma neurofilament light (NfL) levels, and positively correlated with gray matter volume in the hippocampus, parahippocampal gyrus, and right lateral temporal lobe. The availability of mGluR5 in

the hippocampus and parahippocampal gyrus was also positively correlated with global cognition scores on the Mini-Mental State Exam and Montreal Cognitive Assessment. Because this study was exploratory with a small sample size, there were no statistical corrections for multiple comparisons.

Studies using other PET tracers for mGluR5 have observed similar findings. In a PET imaging study using [11C]-ABP688 to measure mGluR5 distribution in 9 Alzheimer's patients and 10 healthy controls, there were no overall differences in mGluR5 signal; however, distribution volume ratio was reduced in the bilateral hippocampus and bilateral amygdala in Alzheimer's patients compared to healthy controls (Treyer et al., 2020). No differences were found in the other 10 regions examined (frontal lobe, temporal lobe, parietal lobe, occipital lobe, insula, anterior cingulum, posterior cingulum, thalamus, putamen, caudate). This study was also exploratory with a low sample size, and therefore comparisons were not corrected for multiple testing. Also, Alzheimer's patients were older than the healthy controls, so the groups were not age-matched. The authors noted that it remains to be determined whether the potential changes in mGluR5 signals are due to synaptic loss, reduction of potential binding sites, or adaptive mechanisms inherent to Alzheimer's disease/pathology.

In another study of 16 people with amnestic mild cognitive impairment or mild Alzheimer's disease and 15 cognitively normal controls, mGluR5 binding measured by [18F]FPEB PET imaging was 43% lower in the hippocampus of Alzheimer's patients compared to cognitively normal people (Mecca et al., 2020). A non-significant trend for lower mGluR5 binding was seen in the association cortical region in Alzheimer's patients compared to cognitively normal controls. Exploratory analyses identified the entorhinal cortex and parahippocampal gyrus as having lower mGluR5 binding in Alzheimer's patients. In the overall study cohort, hippocampal mGluR5 binding was associated with episodic memory performance and inversely associated with global function (measured by CDR-SB).

In post-mortem brain tissue obtained from Alzheimer's disease patients, Aβ oligomers were bound to PrP^{C}; this was not seen in brain tissue from non-demented subjects. This binding was preferential for high molecular weight Aβ oligomers (Dohler et al, 2014; Zou et al, 2011).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

In mice, BMS-984923 has good oral bioavailability (50-90%) and a linear dose response (Haas et al, 2017; Spurrier et al., 2022). At an oral BMS-984923 dose of either 7.5 or 15 mg/kg, the plasma concentration exceeded 2 µM at 10 hours, and brain concentrations were as high as plasma concentrations when measured 3 hours after a 7.5 mg/kg oral dose (Haas et al, 2017).

In a study using [18F]FPEB positron emission tomography (PET) to visualize mGluR5 occupancy, BMS-984923 treatment at well-tolerated doses effectively occupied brain mGluR5 sites in monkeys and mice (Spurrier et al., 2022). In monkeys, single intravenous doses of BMS-984923 (0.03 to 1.0 mg/kg) blocked mGluR5 in the brain in a dose-dependent manner. Receptor occupancy ranged from 27% at the 0.03 mg/kg dose to 94.4 ± 0.4% at the 1.0 mg/kg dose. In mice, a single oral dose of BMS-984923 (7.5 mg/kg) administered 2 hours before [18F]FPEB PET blocked brain mGluR5 with an average receptor occupancy of 98% across brain regions. Mouse brain to plasma ratio ranged from 0.959 at 0.25 hours to 1.9 at 4 hours.

In a mouse model of Alzheimer's disease long after the development of pathology including Aβ plaque, gliosis, synapse loss, and memory impairment (14-month old, APPswe/PS1ΔE9 mice), BMS-984923 treatment (3.75 mg/kg, twice daily, oral gavage) for 4 weeks restored memory deficits measured by the novel object recognition, Morris water maze, and passive avoidance tests (Haas et al, 2017). In wild-type mice, BMS-984923 treatment did not affect cognitive function. In APPswe/PS1ΔE9 mice, BMS-984923 treatment significantly restored synapses (measured by presynaptic SV2A and postsynaptic PSD95) to levels comparable to wild-type mice and prevented the Aβ oligomer-induced signaling abnormalities (activation of Pyk2, CaMKII, and eEF2). BMS-984923 treatment in these mice did not significantly alter amyloid plaque load, astrogliosis, or microgliosis compared to vehicle-treated APPswe/PS1ΔE9 mice. Together, the restoration of cognitive deficits appears to be through recoveries of synapses.

In the double knock-in mouse model of Alzheimer's disease (AppNL-G-F/hMapt double knock-in mice), BMS-984923 treatment for 4 weeks rescued learning deficits, measured by the Morris water maze (Spurrier et al., 2022). The presence and abundance of the presynaptic marker SV2A in the hippocampal dentate gyrus positively correlated with spatial memory performance.

In two aged mouse models of Alzheimer's disease (APPswe/PS1ΔE9 mice and AppNL-G-F/hMapt double knock-in mice), BMS-984923 treatment restored synaptic density, as measured by [18F]SynVesT-1 PET for SV2A and by histology (Spurrier et al., 2022). In 12-13 month-old APP/PS1 mice that had significantly reduced synapses, BMS-984923 treatment for 4 weeks restored synapses in the hippocampus and cortex, measured by presynaptic SV2A and postsynaptic PSD95 markers, to wild-type levels and this effect persisted for at least 4-weeks after treatment cessation (after 4 weeks of drug washout, which is >60 half-lives of BMS-984923). In 12-13 month-old AppNL-G-F/hMapt double knock-in mice, BMS-984923 treatment for 4 weeks increased synapse density by 17% compared to baseline, measured by [18F]SynVesT-1 PET, resulting in synapse density comparable to age-matched wild-type mice.

Accordingly, BMS-984923 treatment restored pre- and post-synaptic markers (SV2A and PSD-95, respectively) in these mice to levels equal to those of age-matched wild-type mice. In both APPswe/PS1ΔE9 mice and AppNL-G-F/hMapt double knock-in mice, BMS-984923 treatment prevented synaptic localization of the complement component C1Q and synaptic engulfment.

In triple-transgenic mice expressing human mutant tau as well as mutant APP and PS1 (3xTg mice), BMS-984923 treatment (7.5 mg/kg/day) for 4+ weeks reduced total tau and insoluble tau to levels comparable to wild-type mice (Haas et al, 2017). BMS-984923 treatment also reduced pathological phospho-Tau (S199/S202) in the hippocampal CA1 area and frontal cortex.

In 12-month-old AppNL-G-F/hMapt double knock-in mice, BMS-984923 treatment for 4 weeks significantly reduced phospho-tau, measured by AT8 (in the cerebral cortex), p-tau-S396/S404 (in the cerebral cortex), and p-tau217 immunoreactivity (in the cerebral cortex and hippocampal CA1) (Spurrier et al., 2022).

In a mouse model of Alzheimer's disease (20-month old, App NL-G-F /hMapt double knock-in mice, after Alzheimer's pathology is well established), BMS-984923 treatment (incorporated into mouse chow) for 2 months reversed the functional connectivity deficits measured by functional MRI (Mandino et al., preprint, 2024).

In two mouse models of Alzheimer's disease, single-nuclei transcriptomics demonstrated that BMS-984923 treatment normalized expression patterns to a far greater extent in neurons than glia (Spurrier et al., 2022). Of Alzheimer's associated genes, 83% and 63% of AD-associated expression changes within excitatory neurons of APP/PS1 and double knock-in brain samples, respectively, were corrected by BMS-984923 treatment. BMS-984923 treatment restored both up-regulated and down-regulated genes. Neuronal differentially expressed genes corrected by BMS-984923 treatment were strongly enriched in gene ontology terms related to neuronal synapses, with less prominently populated networks related to ribosome, V–adenosine triphosphatase (ATPase), and glial projection.

It is worth noting that PrP^C is not the only receptor to bind to Aβ oligomers. Other putative Aβo-binding proteins, most localized at the synapse, include GluN1, GluA2, α7 nicotinic acetylcholine receptor, RAGE, insulin receptor, $p75^{NTR}$, β_2-adrenergic receptors, Fz Wnt receptor, NL1, reelin, GM_1 ganglioside, and LRP1. To address this, Smith et al (2019) conducted a standardized screen with putative Aβ oligomer-binding proteins expressed in non-neuronal cells and found that only three (PrP^C, NgR1, and LilrB2) bound to synthetic Aβ oligomers and Aβ oligomers from Alzheimer's post-mortem brain tissue (only PrP^C

and NgR1 bound to postmortem Aβ oligomers). PrP^C accounted for 50% of the Aβ oligomer binding, while NgR1 and LilrB2 accounted for 20% of the binding, suggesting there is at least one other Aβ oligomer-binding protein. The only receptors found to bind to Aβ oligomers, or alter Aβ oligomer signaling, in unbiased screens include PrP^C, FcγRIIB, and sigma-2/PGRMC1 (Purro et al, 2018).

APOE4 interactions: Unknown

Aging and related health concerns: BMS-984923 has not been explored for the treatment of age-related diseases beyond neurodegenerative conditions.

Types of evidence:

- No clinical or laboratory studies

Based on the mechanism of action, BMS-984923 is not expected to be efficacious for age-related conditions that do not involve the brain.

Safety: A phase I single dose escalation study in healthy older adults has shown that doses up to 200 mg did not cause any serious adverse events and there were no clinically significant changes in safety assessments. Long-term safety has not been established.

Types of evidence:

- 1 open-label phase I study
- Several laboratory studies

In an open-label phase I single dose escalation study in 36 healthy older adults, BMS-984923 at 10, 40, 70, 100, 150, or 200 mg (orally) did not cause any serious adverse events and there were no clinically significant changes in safety assessments (vital signs, physical exam, ECG, and neuropsychiatric inventory) (NCT04805983). Adverse events included oral pain (n=1 with the 40 mg dose), oral paresthesia (n=1 with the 200 mg dose), infusion site bruising (n=2, one person each from the 40 mg and 100 mg dose cohorts), infusion site pain (n=1 with the 100 mg dose), infusion site discomfort (n=1 with the 70 mg dose), increased blood triglycerides (n=1 with the 10 mg dose), increased blood pressure (n=1 with the 10 mg dose), hypercalcemia (n=1 with the 200 mg dose), neck pain (n=1 with the 100 mg dose), headache (n=3, one person each from the 10, 100, and 150 mg dose cohorts), taste disorder (n=1 with the 40 mg dose), presyncope (n=1 with the 70 mg dose), dizziness (n=1 with the 150 mg dose), contact

dermatitis (n=2, one person each from the 70 and 150 mg dose cohorts), and hypertension (n=1 with the 200 mg dose).

In rats, single oral doses of BMS-984923 at 5, 15, and 45 mg/kg did not produce any relevant effects on neurobehavioral function, as evaluated by a modified Irwin test, or on body temperature (Spurrier et al., 2022). In Good Laboratory Practice (GLP) 28-day repeat-dose studies in rats and monkeys, the no-observed-adverse effect level (NOAEL) doses were 15 mg/kg/day for rats, and 200 mg/kg/day for monkeys. BMS-984923 was not mutagenic.

BMS-984923 was tested in 508 binding and cell-based functional assays, and showed no affinity or selectivity (>300-fold) for all targets except for protease-activated receptor 1 and progesterone receptor for which there was a selectivity between 100- and 300-fold relative to the mGluR5 Ki of 0.6 nM (Spurrier et al., 2022). BMS-984923 showed no evidence to be a P-glycoprotein substrate. The IC50's for CYP inhibition were well above efficacious drug concentrations of BMS-984923. BMS-984923 inhibited hERG (human ether-a-go-go related gene) in a GLP cell culture assay with an IC50 of 1.14 µM, which is 1900-fold above the efficacious exposure concentration. During an *in vivo* monkey cardiovascular study at doses up to 200 mg/kg, the QT interval was unaltered, and there were no observed effects on respiratory, central nervous system, or cardiovascular function. Together, oral dosing with BMS-984923 was well tolerated at exposures more than 250-fold greater than required to occupy 50% of the mGluR5 sites in monkeys.

Drug interactions: Drug interactions with BMS-984923 have not been published in peer-reviewed manuscripts.

Sources and dosing:

BMS-984923 (also known as ALX-001) is under clinical development by Allyx Therapeutics for the treatment of neurodegenerative diseases. Dosage has not been established. Phase 1 studies in healthy people and in people with Alzheimer's disease and Parkinson's disease are ongoing and are testing oral doses of 50, 100, and 150 mg, twice daily (NCT05804383; NCT06309147).

Research underway:

There are 3 ongoing clinical trials testing BMS-984923 based on ClinicalTrials.gov. A double-blind randomized placebo-controlled phase 1b study is testing multiple ascending doses of BMS-984923 (50,

100, and 150 mg, twice daily, orally) for up to 28 days in healthy volunteers and in people with Alzheimer's disease to assess its safety and tolerability (NCT05804383). Primary outcomes include incidences of treatment-emergent adverse events, clinically significant laboratory abnormalities, and clinically significant changes in safety assessments. This study is scheduled to be completed in July 2024. A double-blind randomized placebo-controlled phase 1 study is testing the safety of BMS-984923 (50 or 100 mg, orally, twice daily) for 28 days in 18 people with Parkinson's disease (NCT06309147). The primary outcome is incidence of treatment-emergent adverse events. This study is scheduled to be completed in July 2025. An open-label randomized crossover study of BMS-984923 in healthy older adult volunteers is testing food effects, safety, and tolerability (NCT05817643). This study is scheduled to be completed in June 2024.

Search terms:

Pubmed, Google: BMS-984923, ALX-001

Websites visited for BMS-984923, ALX-001:

- Clinicaltrials.gov
- NIH RePORTER
- PubChem
- DrugBank.ca (0)