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.

Duvax

Evidence Summary

In mice, a mixture of AV-1959R and AV1980R using the Multi-TEP platform induces high antibody titers against both Aβ and tau without autoreactive T cell brain infiltration. No data in humans exist to date.

Neuroprotective Benefit: In mice, a mixture of AV-1959R and AV1980R generated Aβ42 and tau antibodies that recognized Aβ plaques and neurofibrillary tangles/neuropil threads in human AD brain sections. No studies have been completed in humans.

Aging and related health concerns: No studies have tested Duvax for age-related conditions aside from Alzheimer's disease.

Safety: In mice, AV-1959R/D and AV1980R/D do not result in toxicities. AV-1959D vaccine did not result in vasogenic edema or microhemorrhages. No clinical trials of the individual vaccines or their combination have been completed in humans.

Availability: in clinical development	**Dose**: not established	**Chemical formula:** N/A **MW**: N/A
Half-life: not documented	**BBB**: penetrant	
Clinical trials: No clinical trials have been completed with Duvax.	**Observational studies**: N/A	

What is it?

Duvax is a vaccine against both Aβ and tau and it is under development by Nuravax. AV-1959R and AV-1980R vaccines target Aβ and tau, respectively. These vaccines are based on the Multi-TEP platform that consists of a string of 12 non-self, pathogen-derived T helper epitopes [the promiscuous PADRE epitope, epitopes from tetanus toxin (P23, P32, P21, P30, P2, P7, P17, and P28), hepatitis B (HBsAg, HBVnc) and the influenza virus (MT)]. The Multi-TEP vaccine platform is designed to provide a broad coverage of human MHC class II polymorphism by using a wide array of foreign pathogen-derived epitopes to evoke a robust T helper cell signal that promotes antibody production. Older people respond poorly to new vaccines due to immunosenescence, while MultiTEP provides a way to promote antibody production by activating not only naïve T helper cells but also pre-existing memory T helper cells previously generated in response to infections and/or vaccines (to tetanus toxin, hepatitis B, and influenza). AV-1959R contains 3 copies of Aβ B cell epitope (Aβ1–11) attached to the MultiTEP. AV-1980R contains 3 copies of tau B cell epitopes (tau2-18) attached to the MultiTEP. The N-terminal region of tau (aa2-18) is the phosphatase activation domain (PAD) that is normally hidden in the native protein in a paperclip-like conformation but becomes exposed during tau aggregation, playing a role in tau polymerization and aggregation-mediated toxicity (e.g., dephosphorylation of the kinesins and dropping of the cargo, inhibiting anterograde fast axonal transport)(Agadjanyan et al., 2017; Hovakimyan et al., 2022).

According to the company website, these vaccines are combined with a novel adjuvant to further boost antibody generation.

Duvax, as well as AV-1959D (Aβ DNA vaccine), AV-1959R (Aβ recombinant vaccine), and AV-1980R (tau recombinant vaccine) are under clinical development for the treatment and/or prevention of

Alzheimer's disease. IND-enabling studies have been completed for the GMP-grade AV-1959D and cGMP grade AV-1980R vaccine with adjuvant (Hovakimyan et al., 2022).

Vaccine development for Alzheimer's disease have failed in the past, partly due to infiltration of autoreactive T cell (and/or antibody) into the brains of vaccinated subjects resulting in meningoencephalitis, as was the case for the AN-1792 clinical trials (Robinson et al., 2004). There was also a substantial portion of vaccinated subjects who were non-responders and most had low antibody titers. Duvax combined with the Multi-TEP platform is designed to overcome self-tolerance by inducing T helper cell responses against foreign epitopes (tetanus, hepatitis B, influenza) while avoiding autoreactive T cells targeting endogenous molecules (e.g., Aβ/Tau).

Neuroprotective Benefit: In mice, a mixture of AV-1959R and AV1980R generated Aβ42 and tau antibodies that recognized Aβ plaques and neurofibrillary tangles/neuropil threads in human AD brain sections. No studies have been completed in humans.

Types of evidence:

- 0 clinical trials
- Numerous laboratory studies

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

No studies have tested Duvax in humans as of February 2025.

Human research to suggest benefits to patients with dementia:

No studies have tested Duvax in humans as of February 2025.

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

In bigenic mice that develop aggressive Aβ and tau pathology (Tau22/5xFAD mice), administration of a mixture of MultiTEP epitope vaccines, AV-1959R (Aβ vaccine, 20 µg/per mouse/per injection, i.m.) and AV-1980R (tau vaccine, 20 µg/per mouse/per injection, i.m.), at 2, 3, 4.5, and 6 months of age generated high Aβ42- and tau(2-18)-specific antibody titers that recognized senile plaques and neurofibrillary

tangles/neuropil threads in human Alzheimer's brain sections (Davtyan et al., 2019). The vaccines were formulated with AdvaxCpG adjuvant (Vaxine Pty Ltd., Adelaide, Australia). Within the brains of Tau22/5xFAD mice, the AV-1959R/AV-1980R combination significantly reduced the levels of soluble and insoluble total tau, and hyperphosphorylated tau as well as insoluble Aβ42. The humoral response in vaccinated mice was high, ranging from 55 to 4785 µg/ml. However, the average concentrations of anti-Aβ antibodies were significantly lower in Tau22/5xFAD mice immunized with the AV-1959R/AV-1980R combination compared to those vaccinated with the AV-1959R vaccine alone.

In Tau22/5xFAD mice immunized with the amyloid vaccine AV-1959R, there was a significant reduction in both soluble and insoluble levels of Aβ42 (Davtyan et al., 2019). Mice immunized with the combination vaccine showed a significant reduction of insoluble Aβ42, but when these cohorts were analyzed by sex, there was a significant reduction of soluble Aβ42 in female mice that received the combination vaccine, but not when they received the AV-1959R alone, while male mice showed significant reduction of soluble Aβ42 with AV-1959R alone but only a slight trend of reduction with the AV-1959R/1980R combination. Insoluble Aβ42 was significantly reduced in male mice with AV-1959R alone or the AV-1959R/1980R combination, but insoluble Aβ42 was non-significantly reduced in female mice.

Tau22/5xFAD mice immunized with AV-1980R or the combination of AV-1959R/AV-1980R showed significant reductions in total and phosphorylated soluble tau (Davtyan et al., 2019). In Tau22/5xFAD mice, there was also a significant reduction in several p-tau species with AV-1959R alone, suggesting that lowering Aβ42 also led to a decrease of tau pathology.

It is worth nothing there appears to be sex-dependent effects of these vaccines in Tau22/5xFAD mice. Vaccinated female mice showed a non-significant reduction in insoluble Aβ42 and tau molecules, while a significant reduction was observed in male mice (Davtyan et al., 2019). The AV-1959R/AV-1980R vaccines did not significantly affect astrocytic activation (GFAP), microglial homeostatic marker (P2RY12), or the myeloid activation marker (CD45) compared to controls. The authors speculate that Aβ and tau antibodies may activate microglia via Fc-mediated signaling, offsetting any potential decrease in glial/microglial activation.

In mice (C57BL/6 mice), different vaccines [Aβ vaccine (AV-1959R), tau vaccine (AV-1980R), and Aβ/tau dual-epitope (AV-1953R)] combined with a variety of adjuvants (AdvaxCpG, delta inulin, Alhydrogel, Montanide-ISA51, Montanide-ISA720, MPLA-SM pharmaceutical grade adjuvants) were tested and the formulation of AV-1959R (20 µg/per injection, i.m., 4 times biweekly) with AdvaxCpG (1 mg/injection)

induced the highest cellular and humoral immune responses with a low variability in responses between animals compared to other adjuvants (Davtyan et al., 2016). Specifically, the mice receiving the AdvaxCpG adjuvant produced strong T cell responses, measured by significantly higher frequencies of IFN-γ+ and IL-4+ T helper cells (specific to foreign Th cell epitopes in the MultiTEP platform) than the vaccines with other adjuvants. In brain homogenates, AV-1959R-immune sera bound monomeric Aβ in soluble fraction and low and high molecular weight Aβ oligomers in both soluble and insoluble fractions. AV-1980R-immune sera recognized monomeric tau as well as multiple larger and smaller species of tau in both soluble and insoluble fractions of brain homogenates.

The dual-epitope vaccine AV-1953R showed robust anti-Aβ antibody titers similar to mice vaccinated with AV-1959R or AV-1959R/AV-1980R combination, but anti-tau titers were significantly lower with AV-1953R compared to the AV-1980R or AV-1959R/AV-1980R (Davtyan et al., 2016). Antibodies generated by the mixture of vaccines (AV-1959R/AV-1980R) or the dual-epitope vaccine (AV-1953R) recognized the same species of Aβ and tau that were detected by antisera isolated from mice vaccinated with appropriate single vaccines (AV-1959R and AV-1980R). When mice are immunized with AV-1959R formulated in AdvaxCpG and boosted with the tau vaccine AV-1980R, cellular and humoral immune responses were significantly higher than sham-boosted mice.

Aβ vaccine (AV-1959R, AV-1959D):

In mice, the anti-Aβ AV-1959D DNA-based vaccine, which encodes 3 copies of Aβ B cell epitope (Aβ1–11) fused to the MultiTEP platform and is delivered by electroporation, generated a robust cellular immune response to foreign epitopes and induced high levels of anti-Aβ antibodies in all mice, but avoided activation of potentially harmful autoreactive T cells (Davtyan et al., 2014). Mice were injected with AV-1959D (25 or 50 µg) in right flank near the base of the tail. Immediately after AV-1959D administration, electroporation was applied using the AgilePulse™ device. In female mice immunized with the 25 µg dose, there was a significantly higher humoral immune response than in males on days 76 (32 days after the 3rd immunization and 2 days after the 4th) and 158 (84 days after the final immunization). Antibody levels in male mice appear to decline faster than in female mice.

In a mouse model of Alzheimer's disease with established vascular and parenchymal Aβ pathology and prone to cerebral amyloid angiopathy (10-11-month old Tg-SwDI mice), administration of 4 repeated high doses of AV-1959D vaccine (50 µg doses, intradermal, days 1, 14, 44, and 74) led to generation of anti-Aβ antibodies in all mice (Petrushina et al., 2020).

Non-human primates have highly polymorphic MHC class II molecules similar to humans and have the same Aβ sequence as humans. In a study in macaques, the anti-Aβ AV-1959D vaccine and the AV-1955D vaccine (both of which are DNA-based epitope vaccines) activated a broad repertoire of T helper cells specific to the Multi-Tep platform, but did not stimulate potentially harmful autoreactive T cells (Davtyan et al., 2014). The initial doses of AV-1955D were 0.2 (low dose) or 2 mg (high dose) in each leg, i.m., followed by electroporation. After an 18-week resting period, the low-dose group (n=5) switched to receive vaccinations with high-dose AV-1959D (at weeks 44 and 48), while macaques in the high-dose group (n=5) continued to receive high-dose AV-1955 at weeks 44 and 48. Both AV-1955D and AV-1959D vaccines were equally effective in stimulation of anti-Aβ antibody production. Humoral immune responses were long-lasting, with antibodies detected in 7 out of 10 macaques 1.2 years after the last immunization (4 of 5 animals in the AV-1955 immunized group with titers 1:275, 1:550, 1:550, and 1:1100, and 3 of 5 animals in the AV-1959 immunized group with titers 1:137.5, 1:137.5, and 1:250). One macaque that received low-dose AV-1955 followed by high-dose AV-1959 (8 mg total) responded poorly to vaccinations, almost failing to respond to the first set of AV-1955, suggesting that this macaque may have had an immunodeficiency.

Tau vaccine (AV-1980R, AV-1980D):

In a mouse model of tauopathy/frontotemporal dementia (THY-Tau22 tg mice), administration of the anti-tau DNA vaccine AV-1980D (20 µg per leg, i.m.), based on the MultiTEP platform and followed by electroporation (AgilPulse device, BTX Harvard Apparatus), induced activation of T helper cells specific to the MultiTEP platform and triggered robust humoral immunity response towards tau, and the immune sera bound to neuritic threads and neurofibrillary tangles in postmortem human Alzheimer's disease brain tissue (Davtyan et al., 2017). AV-1980D was administered at 3, 3.5, 4.5, 5.5, 6.5, 7.5, and 8.5 months of age. No autoreactive T helper cell responses specific to endogenous tau species was detected. Maximum titers of anti-tau antibodies were reached after 2 immunizations (246.5 ± 119.8 µg/ml) and remained slightly lower but steady during 5 subsequent monthly immunizations. The levels of IgG1, IgG2ab, and IgG2b immune responses were robust and stable, while the level of IgM was low. AV-1980D followed by electroporation significantly reduced levels of soluble and insoluble total tau and some species of phospho-tau (insoluble pS199 and soluble AT180) levels in brain extracts but did not significantly alter other phospho-tau species (AT100, pS396, pS404, pS422, AT180, pT212, AT8, and AT270). In a brain tissue staining study, AV-1980D showed a non-significant trend for reducing total tau (p=0.056) and phospho-tau (pS199; p=0.185). Sera from AV-1980D-vaccinated THY-Tau22 mice recognized monomeric and oligomeric forms of tau.

In a different mouse model of aggressive tauopathy/frontotemporal dementia (PS19 mice expressing the P301S mutant form of human tau, first detected at 1.5 months of age), administration of the tau AV-1980R vaccine (20 µg/per injection, i.m.) formulated with the AdvaxCpG adjuvant (1 mg/injection) at 1.5, 2.5, 4, and 6.5 months of age induced high antibody responses (ranging from 276-5,086 µg/ml), with the resulting sera recognizing neurofibrillary tangles and plaque-associated dystrophic neurites in postmortem Alzheimer's disease brain sections (n=2)(Hovakimyan et al., 2019). The AV-1980R with AdvaxCpG produced high concentrations of anti-tau antibodies after 2 immunizations. After the third and fourth immunizations, the mice showed slight reductions in antibody titer, while remaining high. AV-1980R with AdvaxCpG produced equally high levels of IgG1, IgG2ab, and IgG2b antibodies, while the level of IgM was negligible. In PS19 mice, vaccination with AV-1980R/AdvaxCpG also prevented age-related motor deficits (measured by the rotarod test) and cognitive deficits (measured by the Y-maze test, novel object recognition test, and novel place recognition test) compared to controls.

AV-1980R/AdvaxCpG vaccination in PS19 mice also significantly reduced insoluble total tau and phosphorylated tau (pS396 by 41%). Immune sera bound monomeric and oligomeric forms of tau in brain extracts from non-Alzheimer's disease control (tangle stage 2), mild cognitive impairment (tangle stage 1), mild Alzheimer's (tangle stage 4), moderate Alzheimer's (tangle stage 5), and severe Alzheimer's (tangle stage 6) cases, based on Western blot (Hovakimyan et al., 2019). AV-1980R/AdvaxCpG vaccination in PS19 mice also significantly decreased PAD-exposed tau (i.e., aggregated tau) and glial activation (measured by GFAP expression), without affecting microglial activity (measured by IBA-1 expression).

Non-human primates have highly polymorphic MHC class II molecules similar to humans and show 98% tau homology with humans (the sequence of the tau2-18 region differs from human tau by only one residue). In cynomolgus monkeys (11-18 years old), administration of the tau vaccine AV-1980R (100 µg) formulated in AdvaxCpG adjuvant at weeks 0, 2, 6, 26, and 46 resulted in activation of a broad repertoire of MultiTEP-specific T helper cells, which then activated B cells producing antibodies to the tau epitope, resulting in high titers of anti-tau antibodies in all vaccinated monkeys (Hovakimyan et al., 2022). The average concentration of antibodies calculated based on anti-tau2-18 humanized mAb was 232±67 µg/ml. All vaccinated animals produced IgG antibodies specific to human tau protein, with negligible IgM. There was no induction of potentially harmful autoreactive T helper cells against tau in the immunized monkeys. The resulting anti-tau IgG antibodies recognized pathological tau tangles and tau-positive neuritis in postmortem brain sections from Alzheimer's patients (but not in control non-Alzheimer's brain sections). IgG antibody responses peaked after the third immunization, then slightly decreased through week 20. The fourth immunization at week 26 boosted the antibody production that

persisted at the same level up to week 55. The AV-1980R with AdvaxCpG activated an extensive repertoire of Th cells specific to Multi-TEP in all monkeys, but each monkey responded to a particular set of epitopes, with the same Th epitope stimulating strong, mediocre, weak, or no cellular responses depending on the monkey.

APOE4 interactions:
Unknown

Aging and related health concerns: No studies have tested Duvax for age-related conditions aside from Alzheimer's disease.

Types of evidence:

- 0 clinical trials
- 0 laboratory studies

Safety: In mice, AV-1959R/D and AV1980R/D do not result in toxicities. AV-1959D vaccine did not result in vasogenic edema or microhemorrhages. No clinical trials of the individual vaccines or their combination have been completed in humans.

Types of evidence:

- 0 clinical trials
- Numerous laboratory studies

Safety and toxicity studies of anti-Aβ (AV-1959R, AV-1959D) and anti-tau vaccines (AV-1980R, AV-1980D) have been carried out individually. No clinical trials of the individual vaccines or the combination have been completed in humans as of February 2025.

Studies of IND-enabling biodistribution and safety/toxicology of cGMP-grade AV-1959D amyloid vaccine (delivered by electroporation) have been completed (Petrushina et al., 2020). In a mouse model of Alzheimer's disease (Tg2576 mice), biodistribution studies 2 days after a high-dose AV-1959D injection (50 µg) demonstrated high copy numbers of AV-1959D plasmid after single immunization at the injection site (ranging from 3794 to 185,292,500 copies) but not in the tissues of distant organs. Plasmids persisted at the injection sites for 60 days after vaccination in some mice. High variability in

plasmid copy numbers at the injection site may be associated with skin tissue susceptibility to electrical pulses across mice. Plasmid copy numbers in distant organs in female and male mice did not exceed 100 copies/µg of genomic DNA except in bone marrow from one male mouse and inguinal lymph nodes from another male mouse in which the copy numbers were slightly higher than 100. The most important concern associated with DNA vaccines is the possible integration of the plasmid into the chromosome, and integration studies are warranted when plasmid persists in any tissue of any animal at 30,000 copies per µg of host DNA. On the 60th day after the injection, 5626, 5319, 4529, and 151 copies of plasmid per 1 µg genomic DNA were detected in the injection sites of two male and two female mice, respectively, thus plasmid persistence was not analyzed at later time points.

In Tg2576 mice with established amyloid pathology that received 3 doses of AV-1959D, no short- or long-term toxicities were observed (Petrushina et al., 2020). The FDA required testing doses that are lower and higher than the optimal dose (25 µg/mouse), with the high dose at least 10-fold higher than that expected for future clinical trials (dose/kg). These doses, calculated per kg (and not accounting for body surface area; ~200 µg/kg, ~1000 µg/kg and ~2000 µg/kg), are about 14-, 70- and 140-fold higher than the maximal dose expected for use in humans (1000 µg/subject or ~14 µg/kg for human with average weight of 70 kg).

In Tg2576 mice, administration of 4 repeated electroporation-mediated intradermal injections of AV-1959D (5, 25 and 50 µg doses, days 1, 14, 44, and 74), no adverse findings were observed in health observations, food intake, body weights, gross necropsy, absolute organ weights or weight ratios, clinical pathology (hematology/coagulation parameters, clinical chemistry) nor in histopathology data (Petrushina et al., 2020). Only minimal reactions at the injection site were observed. The study duration was 158 days.

Given the past amyloid vaccine trials leading to meningoencephalitis (i.e., AN-1792 active vaccination), the FDA recommended conducting an extensive neuropathology evaluation. One of the adverse events of anti-Aβ immunotherapy in Alzheimer's patients can be cerebral amyloid angiopathy, which may develop due to rapid removal of parenchymal Aβ or triggered when exposed to antibodies against Aβ. In a mouse model of Alzheimer's disease with established vascular and parenchymal Aβ pathology and prone to cerebral amyloid angiopathy (10-11-month old Tg-SwDI mice), administration of 4 repeated high doses of AV-1959D vaccine (50 µg doses, intradermal, days 1, 14, 44, and 74) did not show any immunotherapy-induced vasogenic edema (measured by T2-weighted MRI for edema) or increase microhemorrhages (measured by susceptibility-weighted image MRI and iron staining) on days 2 and 14 after the last immunization (Petrushina et al., 2020). There were no overt differences on any of the T2-

weighted MRI or quantitative T2 maps on days 2 and 14 after the last vaccination. In Tg-SwDl mice, multiple immunizations with AV-1959D did not induce T and B cell infiltration (measured by anti-CD3 and anti-B220 stained cells, respectively), glial activation (measured by GFAP labeling), microglial activation (measured by Iba1-positive microglia), vascular deposition of Aβ, or neuronal degeneration (necrosis and apoptosis, measured by the number of TUNEL-positive and cleaved caspase-3-positive cells, respectively) greater than those in the control group. Whole-brain volumes and ventricular volumes were also not significantly different between immunized and control (PBS-injected) cohorts at 2 or 14 days post vaccine administration.

In cynomolgus monkeys (11-18 years old), administration of the tau vaccine, AV-1980R (100 μg) formulated in AdvaxCpG adjuvant, at weeks 0, 2, 6, 26, and 46 did not result in any significant differences in general health status compared to control monkeys during the 5 vaccine administrations and at 1-year follow-up (Hovakimyan et al., 2022). Each monkey was observed daily for abnormal appearance and behavior by the veterinarian, visually monitored for signs of diarrhea, dehydration, cuts, lacerations, and others. The cage floor and other structures were also scanned for blood, evidence of birth, diarrhea, and others.

The adjuvant AdvaxCpG was well tolerated by C57BL/6 mice with no evidence of either local or systemic vaccine adverse reactions (Davtyan et al., 2016). There were no harmful autoreactive T helper cells detected after re-stimulation of immune splenocytes with Aβ or tau self-epitopes, measured by ELISpot or splenocyte proliferation assay.

Drug interactions: Drug interactions with Duvax have not been documented.

Sources and dosing:

Duvax is under development by Nuravax, which is licensed for the patented MultiTEP platform technology of prophylactic vaccines.

Research underway:

No clinical trials of Duvax are registered on ClinicalTrials.gov as of February 2025. A phase I randomized double-blind placebo-controlled study of AV-1959D, a DNA vaccine targeting the N-terminal epitope of Aβ, is ongoing (NCT05642429). This study is testing the safety and tolerability of 3 doses of AV-1959D

(500, 1,000, or 2,000 µg) versus placebo in 48 people with early Alzheimer's disease. This trial is estimated to be completed in November 2026.

Search terms:

Pubmed, Google: Duvax, AV-1959, AV-1980

Websites visited for Duvax:

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