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.

CN-105

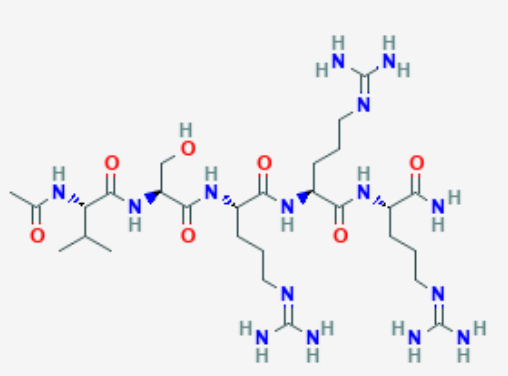
Evidence Summary

Early-phase clinical studies have suggested potential benefit of short-term intravenous CN-105 treatment for preventing postoperative delirium and improving intracerebral hemorrhage.

Neuroprotective Benefit: Early-phase clinical trials have suggested potential benefit of CN-105 in preventing POD and treating intracerebral hemorrhage. Studies in various preclinical models suggest CN-105 improves function and reduces neuroinflammation.

Aging and related health concerns: CN-105 has not been studied in peripheral age-related conditions.

Safety: Intravenous treatment of CN-105 (every 6 hours) for up to 3 days has been well-tolerated with adverse event rates appearing lower than for placebo. There have been no concerning changes in ECG, vital signs, or clinical laboratory tests.

Availability: not available; in clinical development	**Dose**: not established; doses up to 1.0 mg/kg, intravenously, every 6 hours have been tested in clinical trials	**Chemical formula:** $C_{28}H_{55}N_{15}O_7$ **MW**: 713.8  Source: PubChem
Half-life: termination half-life of ~3.6 hours	**BBB**: penetrant	
Clinical trials: The largest randomized controlled trial to date enrolled 137 surgery patients.	**Observational studies**: none available	

What is it?

CN-105 is a small pentapeptide developed from the apolipoprotein E (APOE) receptor-binding domain. ApoE is the primary apolipoprotein produced in the brain and its secretion is upregulated after injury (van Wyck et al., 2022). Endogenous APOE modulates glial activation and neuroinflammatory responses and these effects are mediated, in part, by the APOE receptor-binding domain interacting with the low-density lipoprotein receptor-related protein-1 (LRP1), a scavenger receptor present on microglia and neurons (Pocivavsek et al., 2009). Endogenous APOE does not cross the blood-brain barrier, and therefore, smaller APOE mimetic peptides such as CN-105 were designed from the receptor-binding region (Laskowitz et al., 2017). CN-105 inhibits microglial activation and inflammation (Tu et al., 2017) and has been studied in people with intracerebral hemorrhage as a therapeutic intervention (James et al., 2022) as well as in people undergoing surgery for the prevention of postoperative delirium (Timko et al., 2026).

Neuroprotective Benefit: Early-phase clinical trials have suggested potential benefit of CN-105 in preventing POD and treating intracerebral hemorrhage. Studies in various preclinical models suggest CN-105 improves function and reduces neuroinflammation.

Types of evidence:

- 1 randomized controlled trial for POD/POCD prevention
- 1 open-label trial in people with intracerebral hemorrhage
- 2 exploratory biomarker studies of clinical trials (MARBLE and CATCH)
- Numerous laboratory studies

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

Postoperative delirium: Postoperative cognitive dysfunction and delirium (POCD, POD, respectively) occur in up to 40% of the 16+ million people over the age of 60 who undergo surgery each year. In a phase 2 triple-blind randomized placebo-controlled trial (MARBLE trial) testing an escalating dose of CN-105 (0.1, 0.5, or 1 mg/kg, i.v. started before surgery and every 6 hours for up to 3 days) in 186 patients receiving non-cardiac and non-intracranial surgery, the postoperative delirium incidence was 19.3% (26 out of 135) with CN-105 compared to 26.5% in the placebo arm (13 out of 49) (OR=0.66; 95% CI, 0.31 to 1.42; p=0.29)(Timko et al., 2026). With regards to delirium severity, in a univariable proportional odds model, the odds ratio (OR) for an increase in delirium severity in the CN-105 vs placebo groups was 0.66 (95% CI, 0.37 to 1.20, p=0.18). In a multivariable proportional odds model, the OR was 0.69 (95% CI, 0.37 to 1.28, p=0.24). CN-105 had no significant effects compared to placebo on cognitive functions, measured by the global Continuous Cognitive Index change from before surgery to 6 weeks post-surgery. There was also no effect of CN-105 on individual cognitive domain score changes over this period. The rate of mild postoperative neurocognitive disorder was 14.8% (16 out of 108) in the CN-105 group and 17.1% (6 out of 35) in the placebo group. There were no instances of major postoperative neurocognitive disorders in this study.

CN-105 was detectable in the cerebrospinal fluid (CSF) in proportionately increasing levels across the 3 dose groups (4.8 ng/mL in the CSF and 151 ng/mL in the plasma with the 0.1 mg/kg dose; 29.1 ng/mL in the CSF and 685.4 ng/ml in the plasma with the 0.5 mg/kg dose; 60.2 ng/mL in the CSF and 1448.6 ng/mL in the plasma with the 1.0 mg/kg dose)(Timko et al., 2026). CN-105 treatment numerically reduced several cytokines in the CSF when comparing preoperative to 24 hours post-surgery; however, none of these were statistically significant. IL-6 was numerically reduced by 0.39 pg/mL (95% CI, -0.93 to

0.14 pg/mL, p=0.12), G-CSF was reduced by 0.84 pg/mL (95% CI, -3.06 to 1.40 pg/mL; p=0.18), IL-8 was reduced by 23.32 pg/mL (95% CI, -94.36 to 44.93 pg/mL; p=0.57), and MCP-1 was reduced by 2.36 pg/mL (95% CI, -58.57 to 58.62 pg/mL; p=0.50). There were no significant differences in preoperative to postop changes between groups in CSF Alzheimer's biomarkers, including tau, ptau181, or Aβ42.

A CSF proteome study of the MARBLE trial found that of the 2,086 proteins examined, 881 (42.2%) showed a change after surgery (p-FDR<0.05)(Zou et al., 2025 preprint). The 5 most significantly upregulated CSF pathways were negative regulation of smooth muscle cell migration, negative regulation of endothelial cell apoptotic process, extrinsic apoptotic signaling pathway via death domain receptors, regulation of extrinsic apoptotic signaling pathway via death domain receptors, and smooth muscle cell migration. The 5 most significantly downregulated CSF pathways were regulation of non-canonical NFκB signal transduction, negative regulation of leukocyte apoptotic process, sulfur compound metabolic process, proteoglycan metabolic process, and leukocyte apoptotic process. CN-105 treatment did not have any significant effects on 24-hour postoperative changes in CSF protein levels (p-FDR>0.05 for all). This was the case in univariate models as well as in multivariable models adjusted for numerous baseline patient characteristics and surgery type. After FDR adjustment, there was no significant effect of APOE4 carrier status on CSF protein levels at baseline or 24 hours post-surgery. The authors noted that because of the large number of CSF proteins examined, the burden of false discovery rate-based multiple testing correction was very high, which may have reduced the power to detect effects of CN-105 or APOE4 on CSF protein or pathway levels. The authors do not rule out the possibility that CN-105 has an effect on CSF protein levels post-surgery.

Intracerebral hemorrhage: Spontaneous nontraumatic intracerebral hemorrhage accounts for 10-15% of all strokes and nearly half of afflicted patients die within 30 days of the hemorrhage. APOE is a key mediator of neuroinflammatory response and recovery from brain injury (Lynch et al., 2002; Lei et al., 2012). In an open-label trial (CATCH) of 38 patients with acute primary supratentorial intracerebral hemorrhage, CN-105 treatment (1.0 mg/kg, i.v., every 6 hours) started within 12 hours of symptom onset and continued for up to 3 days was associated with improved modified Rankin scale (mRS) at 30 days after hemorrhage when compared with a closely matched natural history cohort (James et al., 2022). Over the course of CN-105 treatment, NIH Stroke Scale (NIHSS) improved from median (range) of 12.0 (4.0 to 25.0) to 8.5 (1.0 to 29.0). There were no significant effects of CN-105 on hematoma volume, which is consistent with its mechanism of action of reducing neuroinflammation. Because of the open-label design and an absence of a placebo group, placebo effects cannot be ruled out. The study results cannot tease apart the effects of the CN-105 versus the natural recovery trajectory.

Human research to suggest benefits to patients with dementia:

No studies have tested the effects of CN-105 in people with dementia.

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

Alzheimer's disease models: In a mouse model of Alzheimer's disease (male APP/PS1/APOE4 mice), CN-105 treatment (4 mg/kg/day, s.c.) for 40 days reduced Aβ pathology and memory deficits (measured by Morris water maze and contextual fear conditioning) when the treatment was initiated at 14-18 weeks of age, early in the disease course (Krishnamurthy et al., 2020). CN-105-treated mice showed a 2-fold increase in the amount of time spent in the platform location compared to vehicle-treated controls during the probe trial of the Morris water maze test. However, the same treatment but initiated at 25-28 weeks did not reduce amyloid pathology and showed no difference in the time spent on the platform during the probe trial of the Morris water maze test. CN-105-treated 25-28-week-old male APP/PS1/APOE4 mice did show improved performance on the contextual fear conditioning test compared to vehicle-treated mice. These findings suggest that the beneficial effects of CN-105 in Alzheimer's models may be a function of age/pathology and the optimal therapeutic window for treatment with CN-105 is in the early phase of the disease.

Stroke models: Glutamatergic excitotoxicity is one of the key mechanisms for neurodegeneration in stroke. In a rat model of transient ischemic stroke, CN-105 treatment (0.1 to 0.4 mg/kg) significantly reduced infarct volume similar to the rats given the free-radical scavenger edaravone (Xue et al., 2022). At the infarct margin of the primary somatosensory cortex, CN-105-treated rats had higher α7-nAChR+ cells and neuronal counts (NeuN+ cells) compared to vehicle-treated rats. Cell culture studies demonstrated that CN-105 dampens presynaptic glutamate release by nAChR inhibition and there are direct interactions between APOE/derivatives and ion channels.

After ischemic stroke, blood-brain barrier disruption occurs and APOE-deficient mice have compromised blood-brain barrier that is further disrupted after injury (Methia et al., 2001). In a mouse model of ischemic stroke (transient middle cerebral artery occlusion), CN-105 (0.1 mg/kg via tail vein injection) administered 30 minutes post-reperfusion significantly improved survival (75% vs 25%, p=0.013) and reduced infarct volume (by 34-38% depending on the occlusion model) 3 days post-stroke compared to vehicle treatment (Tu et al., 2017). An additional dose of CN-105 at 4.5 hours post-reperfusion maintained the survival benefit but did not further increase it. CN-105 treatment also significantly improved functional outcomes, as measured by rotarod latency and 4-limb wire hanging test. The

improvement was observed as early as the first day post-injury and the benefit was maintained up to 7 days. CN-105 treatment also significantly reduced microglial cell density compared to vehicle. However, when CN-105 was administered beyond the 30-minute post-reperfusion window, no significant functional improvement was observed.

In a mouse model of intracerebral hemorrhage, CN-105 treatment (0.05 mg/kg via tail vein injection) within 24 hours after hemorrhage significantly improved vestibulomotor performance (measured by rotarod latencies) on days 1-5 post-intracerebral hemorrhage (Lei et al., 2016). CN-105 treatment also led to long-term improvement in cognitive function, measured by reduced latencies on the Morris water maze on days 29-32 post-hemorrhage. CN-105 treatment also significantly reduced edema (measured by brain water content) and neuroinflammation (measured by immunohistochemistry of a macrophage/microglia marker, F4/80) in the hippocampus, while promoting hippocampal neuronal survival (measured by unbiased stereology). CN-105 treatment did not affect hemorrhage/hematoma volume or expansion.

Hypertension is the most significant risk factor for non-lobar intracerebral hemorrhage and plays a major role in pathology post-hemorrhage, including cerebral edema and secondary neuronal injury (Bhatia et al., 2012). In spontaneously hypertensive male mice undergoing intracerebral hemorrhage (induced by collagenase injection), CN-105 treatment (at 2, 4, and 24-hour post-hemorrhage) showed a significant dose-dependent effect on vestibulomotor function, and at the highest dose tested (0.20 mg/kg), CN-105 significantly improved neuroseverity scores and reduced ipsilateral brain edema. In spontaneously hypertensive female rats, CN-105 (0.05 mg/kg) had a significant effect on vestibulomotor function and neuroseverity scores and reduced contralateral edema expansion. Age is also a major determinant for intracerebral hemorrhage outcomes. In 11-month-old male mice undergoing intracerebral hemorrhage, CN-105 treatment (at 2, 4, and 24-hour post-hemorrhage) significantly improved vestibulomotor function but not neuroseverity scores. Overall, beneficial effects of CN-105 were observed consistently independent of species, sex, or the presence of comorbid hypertension.

Subarachnoid hemorrhage represents a minority of strokes but is a devastating disease with high rates of mortality and morbidity. In a mouse model of subarachnoid hemorrhage, CN-105 treatment (0.05 mg/kg via tail vein injection) given 2 hours after injury and every 12 hours subsequently for 5 days significantly reduced vasospasm, improved body weight loss recovery, and improved vestibulomotor function and neurologic function compared to vehicle-treated mice (Liu et al., 2018). CN-105 treatment also significantly decreased microgliosis (measured by F4/80 immunoreactivity) and neuronal injury and

promoted long-term neuronal survival (measured by unbiased stereology) in the hippocampus after subarachnoid hemorrhage.

In microglial cell culture (C8-B4 murine microglial cells), LPS increased TNF-α production, but this increase was suppressed in the presence of 1 µM/mL concentration of CN-105 (Tu et al., 2017). The percentage of suppression of TNF-α by CN-105 was concentration-dependent with 20%, 34% and 53% suppression observed with 0.1, 0.3 and 1 µM/mL of CN-105, respectively. In a study of phosphoproteomic signatures, CN-105 affected phosphorylation of neuroinflammatory proteins in ischemic stroke. Notable phosphoproteins differentially changed by CN-105 mediate cellular survival, immunity, and blood-brain barrier integrity.

Brain injury models: Acute central nervous system injury triggers neuroinflammation through the release of damage-associated molecular pattern molecules (DAMPs)(Sun et al., 2025). The inflammatory cascade increases secondary neuronal injury, oxidative stress, and cerebral edema. APOE4 is associated with poor outcomes after traumatic brain injury (Teasdale et al., 1997).

In a mouse model of closed-head injury, CN-105 treatment (0.05, 0.2, or 0.8 mg/kg, i.v.) 2 hours after injury significantly improved vestibulomotor performance measured by rotarod latency compared to vehicle treatment (Laskowitz et al., 2017). CN-105 (0.05 mg/kg, i.v.) administered 4 hours post-injury was also associated with significant and durable improvement in vestibulomotor function as well as reduced deficit in cognitive function and better preservation of memory, measured by the Morris water maze at 28 days post-injury. Treatment with CN-105 also significantly reduced microglial activation (measured by F4/80 immunohistochemistry) and degenerating neurons (Fluoro-Jade B+ neurons) in the hippocampus compared to vehicle-treated mice. Gene expression studies showed that CN-105 treatment (0.05 mg/kg, i.v.) administered 2 hours following injury reduced the post-injury upregulation of cytokines (IL-6, IL-1α, IL-10), TLR pathway genes (Tlr6, Myd88, TLR4), and the DNA binding unit of NF-κβ. CN-105 treatment also further increased the injury-induced upregulation of some genes, including Ccl22 and IL-7, which are associated with recovery and repair. Injury-associated downregulation of Bcl6 was reversed to above sham levels by CN-105 treatment. Together, CN-105 has an overall effect of downregulating neuroinflammation in response to traumatic brain injury.

In a mouse model of closed-head injury, CN-105 treatment (0.2 mg/kg, i.v.) 10 or 20 minutes *prior to* injury improved vestibulomotor function and reduced microglia count in the hippocampus compared to vehicle-treated mice (van Wyck t al., 2022). Functional benefit was also seen when CN-105 (0.05 mg/kg, i.v.) was administered 30 minutes prior to injury, but no benefit was seen when CN-105 was

administered 60 minutes prior to injury. The rationale for testing pretreatment of CN-105 (CN-105 administered prior to injury) was to assess its efficacy as a prophylaxis for soldiers at high risk for traumatic brain injury.

APOE4 interactions:

APOE4 is both a risk factor for Alzheimer's disease and delirium. In a phase 2 triple-blind randomized placebo-controlled trial testing the efficacy of CN-105 (0.1, 0.5, or 1 mg/kg, i.v. started before surgery and every 6 hours for up to 3 days) in preventing postoperative delirium in 186 patients receiving surgery, there was no effect of APOE4 carrier status in delirium incidence or delirium severity (Timko et al., 2026).

APOE4 has been associated with poor functional outcomes in a number of acute brain injuries including subarachnoid hemorrhage (Lanterna et al., 2007). However, no clinical trials have assessed whether CN-105 treatment has differential effects for brain injuries and strokes in APOE4 carriers versus non-carriers.

Aging and related health concerns: CN-105 has not been studied in peripheral age-related conditions.

Types of evidence:

- 0 clinical trials
- 0 laboratory studies

While other APOE mimetics (e.g., COG112) have been tested in models of systemic inflammation, including colitis (Singh et al., 2008), CN-105 has only been studied in central nervous system indications to date.

Safety: Intravenous treatment of CN-105 (every 6 hours) for up to 3 days has been well-tolerated with adverse event rates appearing lower than for placebo. There have been no concerning changes in ECG, vital signs, or clinical laboratory tests.

Types of evidence:

- 1 phase 2 randomized controlled trial in surgery patients
- 1 open-label trial in people with intracerebral hemorrhage
- 2 phase I clinical trials
- Several laboratory studies

In a phase 2 triple-blind randomized placebo-controlled trial 186 patients receiving non-cardiac and non-intracranial surgery (MARBLE), CN-105 (0.1, 0.5, or 1 mg/kg, i.v.) started before surgery and every 6 hours for up to 3 days resulted in fewer grade 2 or higher adverse events compared to placebo (76.6% for CN-105, 87.8% for placebo)(Timko et al., 2026). Serious adverse event incidence was also lower in the CN-105 group than the placebo group (8% vs 22.4%, p=0.007). The CN-105 group had a numerically lower relative risk of grade 2 or higher adverse events within the renal and urinary systems (RR=0.36, p=0.04) and nervous system (RR=0.40, p=0.04) compared to the placebo group. The CN-105 group also had a numerically lower incidence of serious adverse events within the vascular system (RR=0.09, p=0.02) and respiratory/thoracic/mediastinal systems (RR=0.09, p=0.02). There were no deaths in either group during the study follow-up.

In an open-label trial (CATCH) of 38 patients with acute primary supratentorial intracerebral hemorrhage, CN-105 treatment (1.0 mg/kg, i.v., every 6 hours) started within 12 hours of symptom onset and continued for up to 3 days was safe with serious adverse events and adverse events occurring at a rate expected from other similar clinical trials (James et al., 2022). CN-105 was not associated with an increase in hematoma expansion or unanticipated neurological deterioration. CN-105 did not significantly change vital signs and electrocardiogram parameters. Clinical chemistry, blood counts, coagulation profiles, and lipid parameters were stable and did not change significantly throughout the course of the study. There were 14 nonfatal serious adverse events experienced by 12 (32%) participants, most commonly in the nervous system and respiratory disorders. The most commonly experienced treatment-emergent adverse events were pain (29%), constipation (26%), leukocytosis (24%), hypophosphatemia (21%), hypomagnesemia (18%), hyponatremia (18%), nausea (18%), and pyrexia (16%). Eleven treatment-emergent serious adverse events were experienced by 9 (24%) participants and were deemed "unlikely related" to study drug.

In a phase I double-blind placebo-controlled trial of 48 healthy people from the US, single and repeated doses (every 6 hours for 72 hours) of CN-105 (0.01, 0.03, 0.1, 0.3, and 1.0 mg/kg administered i.v. over 30 minutes) resulted in mild transient adverse effects, including headache (0% with placebo, 6% with CN-105) and bradycardia (17% with placebo, 11% with CN-105)(Guptill et al., 2017). The bradycardia was not treatment-emergent. There were no serious adverse events and there were no concerning changes in serial ECG, vital signs, or clinical laboratory tests. Pharmacokinetics analysis revealed linearity without significant drug accumulation. The median half-life in the terminal elimination phase of CN-105 following single or repeated dosing regimen did not change and was approximately 3.6 hours.

In another phase I double-blind placebo-controlled trial, 40 healthy Chinese adults were enrolled to test single and multiple doses of CN-105 (0.03, 0.1, 0.3, or 1 mg/kg, 4 times daily for 13 doses), and pharmacokinetic properties of CN-105 were comparable to those observed in US participants (Li et al., 2022). CN-105 was well-tolerated in healthy Chinese people. A total of 13 adverse events were reported in 30% of subjects (6 out of 8 with the 0.03 mg/kg dose, 1 out of 8 with the 0.1 mg/kg dose, 2 out of 8 with the 0.3 mg/kg dose, 0 out of 8 with the 1.0 mg/kg dose, and 3 out of 8 with the placebo). All adverse events were mild or moderate in severity and self-limited, with no observed dose relationship. Twelve adverse events, corresponding to 12 subjects, were deemed as "possibly related" to the investigational drug. The most common adverse event was increased serum bilirubin (6 out of 12 subjects) and was not dose-dependent. There were no clinically significant physiologic abnormalities or changes in clinical laboratory test values except for the few abnormal laboratory values and ECG abnormalities that were reported as adverse events.

Results from the rodent and beagle Good Laboratory Practice safety and toxicology studies demonstrated that repeated intravenous administration of CN-105 at 5 mg/kg/dose (100-fold the therapeutic dose identified in preclinical efficacy studies), 4 times per day (20 mg/kg/day) for 14 days was well-tolerated, and the 20 mg/kg daily dose was identified as the no observed-adverse effect-level (NOAEL) (Guptill et al., 2017). The 14-day NOAEL in Sprague-Dawley rats was 30 mg/kg/day, equivalent to 4.8 mg/kg/day in humans (Li et al., 2022).

In cynomolgus monkeys, supratherapeutic dosing of CN-105 several orders of magnitude higher than doses studied in humans resulted in symptoms of mydriasis (pupil dilation) and ptosis (Xue et al., 2022). Recovery to normal activity took about 2 serum clearance half-lives of CN-105. In C57BL6 mice, CN-105 had an LD80 of 25 mg/kg with symptoms of spasm and respiratory suppression. With intubation and mechanical ventilation, dosing of 50 mg/kg was not associated with mortality but led to extended sedation after removal of isoflurane anesthesia.

Drug interactions: Drug interactions with CN-105 have not been documented.

Sources and dosing:

CN-105 is under clinical development by AegisCN, LLC, for the treatment of intracerebral hemorrhage, traumatic brain injury, and prevention of postoperative delirium (Duke University press release, April 2026). Doses up to 1.0 mg/kg, intravenously, every 6 hours have been tested in clinical trials (James et al., 2022; Timko et al., 2026).

Research underway:

There are currently no ongoing clinical trials of CN-105 based on ClinicalTrials.gov.

Based on NIHRePORTER, AegisCN, LLC has received funding to test CN-105 for intracranial hemorrhage.

Search terms:

Pubmed, Google: CN-105

Websites visited for CN-105:

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

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