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.

NNI-362

Evidence Summary

NNI-362 was discovered through cell culture screens for the ability to promote neurogenesis. NNI-362 appears to be well-tolerated based on a phase 1a study, and decreased plasma p-tau181 levels.

Neuroprotective Benefit: NNI-362 promoted neurogenesis and improved cognitive function in rodent models. In a phase 1a study in healthy older people, NNI-362 treatment decreased plasma p-tau181 levels.

Aging and related health concerns: Although NNI-362 is under development for "age-related disorders", because of its mechanism of action, it is not likely to have benefits for age-related disorders outside of the brain.

Safety: The phase 1a study in healthy older people suggests that NNI-362 is well-tolerated. Long-term safety is currently unknown.

Availability: in clinical development	**Dose**: A phase 1a dose-escalation study in healthy aged volunteers tested NNI-362 doses of 10 mg, 20 mg, 60 mg, and 120 mg (oral)(NCT04074837).	**Chemical formula:** not published **MW**: not published
Company: NeuroNascent, Inc.		
Half-life: ~12 hours	**BBB**: penetrant based on studies in rodents	
Clinical trials: A phase 1a dose-escalation study of NNI-362 enrolled 56 healthy aged volunteers (NCT04074837).	**Observational studies**: None	

What is it? NNI-362 is under development by NeuroNascent Inc., a privately-held company developing therapeutics aimed at neuronal regeneration. NNI-362 is a lead candidate identified through a phenotypic screen for its ability to promote proliferation of human neuronal progenitor cells and to promote differentiation into mature neurons in a dose dependent manner. NNI-362 exerts these actions through stimulation of p70S6 kinase phosphorylation (downstream of mTOR, a regulator of protein synthesis, mitochondrial biogenesis, and autophagy), which in turn, promotes proliferation and differentiation of neural progenitor cells to neurons (Sumien et al., 2021). NeuroNascent completed a phase 1a study of NNI-362 in healthy older volunteers (NCT04074837) and is planning a phase 1b/2a study in mild to moderate Alzheimer's disease, early Parkinson's disease, and other age-related disorders (NeuroNascent Inc., pipeline).

Neuroprotective Benefit: NNI-362 promoted neurogenesis and improved cognitive function in rodent models. In a phase 1a study in healthy older people, NNI-362 treatment decreased plasma p-tau181 levels.

Types of evidence:

- 1 phase 1a trial
- Several laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:
NNI-362 has not been tested for prevention of dementia or cognitive decline. In a phase 1a study of 56 healthy older people (50-72 years old), NNI-362 treatment at the two highest doses (120 and 240 mg, multiple doses) significantly reduced plasma levels of phospho-tau181 compared to pre-treatment levels (Press release 03/30/2022).

Human research to suggest benefits to patients with dementia:
No evidence exists to date, but NeuroNascent is planning a phase 1b/2a study in mild to moderate Alzheimer's disease, early Parkinson's disease, and other age-related disorders (NeuroNascent Inc., pipeline).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
NNI-362 was identified through a phenotypic screen of small-molecule synthetic libraries that possessed properties conducive to blood brain barrier penetrance and oral administration (NeuroNascent Inc.). These molecules were screened by NeuroNascent for their ability to promote proliferation of human neuronal progenitor cells and to promote differentiation into mature neurons in a dose-dependent manner. These molecules were further optimized with changes to the chemical structure to improve potency in cell culture. These molecules then underwent a secondary screen in cell culture to evaluate whether the molecules were neuroprotective in addition to having neurogenic properties. NNI-362 emerged as the lead candidate. In the *in vitro* screening, NNI-362 at a concentration of 1000 nM promoted neural progenitor cell proliferation on days in vitro (DIV) 3 and increased the ratio of mature neurons to total cells at DIV12/13 (Sumien et al., 2021).

In old mice treated with NNI-362 (1, 3, or 10 mg/kg/day, orally) for 4 weeks, performance on the novel object recognition test was comparable to that of young control mice (Sumien et al., 2021). Old mice had lower numbers of new neurons (BrdU+ cells), while the old mice treated with 10 mg/kg/day NNI-362 had higher numbers of BrdU+ cells than the old vehicle-treated mice. The number of new neurons in the NNI-362-treated mice were not significantly different from the young control mice.

Old mice treated with NNI-362 at 10 mg/kg/day for 4 weeks did not reverse age-related motor dysfunction (Sumien et al., 2021).

In a mouse model of Down Syndrome (Ts65Dn mice), NNI-362 treatment (3 mg/kg/day) reversed the impairment in recognition memory and restored the number of BrdU+ cells surviving in the hippocampal dentate gyrus.

A pilot study also showed that in a model of chronic progressive Parkinson's disease, administration of NNI-362 for a very short duration showed a trend toward regeneration of neuron connections in the caudate putamen while increasing the number of new neuronal progenitors (NeuroNascent Inc., Parkinson's disease).

NNI-362 promotes phosphorylation of the p70S6 kinase (downstream of mTOR), which in turn, promotes proliferation and differentiation of neural progenitor cells to neurons (Sumien et al., 2021). Out of a panel of 151 kinases, NNI-362 exclusively stimulated the p70S6 kinase and allosterically targeted the p70S6 kinase. NNI-362 phosphorylated p70S6 at the neuron regenerative concentration (≥ 1000 nM) and only during the early dividing and beginning differentiation phase (e.g., DIV6), while having no effect in fully differentiated neurons on DIV12. NNI-362 acts at Ser411, the auto-inhibitory pseudosubstrate site, where CDK5 phosphorylates p70S6 kinase during the mitogenic translational stage.

In postmortem studies of Alzheimer's disease patients, neurogenesis has been shown to be reduced in the hippocampal dentate gyrus (Moreno-Jimenez et al., 2019). However, there is continued presence of neural progenitor cells in older people, suggesting that these cells are potential targets for neuroprotection and neuronal regeneration.

Although preclinical studies have so far shown that NNI-362 stimulates neurogenesis, proliferation, survival, and migration of new neurons, future studies are needed to demonstrate that NNI-362 promotes integration of newly formed neurons and synapses with the neurocircuit (Sumien et al., 2021).

APOE4 interactions: Unknown.

Aging and related health concerns: Although NNI-362 is under development for "age-related disorders", because of its mechanism of action, it is not likely to have benefits for age-related disorders outside of the brain.

Types of evidence:

- 0 clinical trials
- 0 laboratory studies

Given that NNI-362 was identified through a phenotypic screen for its ability to promote proliferation of human neuronal progenitor cells, NNI-362 is not likely to have benefits for age-related health conditions outside of the brain.

Safety: The phase 1a study in healthy older people suggests that NNI-362 is well-tolerated. Long-term safety is currently unknown.

Types of evidence:

- 1 phase 1a study
- Several laboratory studies

In a phase 1a single- and multiple-ascending dose study of NNI-362 in 56 healthy older volunteers (age 50-72 years old), NNI-362 administration did not reach a maximum tolerated dose (NCT04074837; 2021 CTAD poster). NNI-362 was administered from 10 to 240 mg orally, once daily, and no serious adverse events or dose-dependent adverse events were observed. There were a total of 17 adverse events in the NNI-362 group (n=42) and 17 adverse events in the placebo group (n=14); all adverse events were mild grade. Any potential drug-related adverse events resolved without concomitant medication. No participants dropped out of the study.

Half-life at 120 mg and 240 mg doses was approximately 12 hours (2021 CTAD poster).

In studies with mice, NNI-362 treatment was suggested to not show toxic or off-target effects after up to 6 weeks of administration; however, details of toxicology and safety data were not presented in the manuscript (Sumien et al., 2021).

Drug interactions: Drug interactions have not been documented.

Sources and dosing: NNI-362 is under clinical development by NeuroNascent Inc. for mild to moderate Alzheimer's disease, early Parkinson's disease, and other age-related disorders (Neuronascent Inc., pipeline). In a phase 1a dose-escalation study in healthy aged volunteers, NNI-362 was administered at doses ranging from 10 to 240 mg, once daily (orally), and no serious adverse events or dose-dependent adverse events were observed (2021 CTAD poster). In mouse models, NNI-362 has been tested at doses ranging between 1-10 mg/kg/day, orally, for up to 6 weeks (Sumien et al., 2021).

Research underway: NeuroNascent is planning a phase 1b/2a study in mild to moderate Alzheimer's disease, early Parkinson's disease, and other age-related disorders (NeuroNascent Inc., pipeline). They propose to enroll 105 patients (age 60-86) who will be randomized to NNI-362 (oral liquid, 120 mg daily) or placebo for 6 months. Proposed primary endpoints are safety and tolerability, and comparison with baseline hippocampal volume (vMRI). Proposed secondary endpoints include OLFACT™ Test Battery or UPSIT, ADAS-cog, MMSE, ADCS-ADL, and plasma phospho-tau.

Intellectual property: NeuroNascent has submitted patent applications for the composition and use of families of structures that promote neurogenesis and neuronal regeneration for neurodegenerative diseases (NeuroNascent Inc.). In 2008, a national patent was filed on lead families for composition and use, including NNI-362. In 2011, USPTO has allowed claims for its patent, "Methods and Compositions for Stimulating Neurogenesis and Inhibiting Neuronal Degeneration", covering composition of NeuroNascent's lead therapeutics (e.g., NNI-362) and chemical family.

Search terms:
Pubmed, Google: NNI-362

Websites visited for NNI-362:

- Clinicaltrials.gov
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com (0)
- WebMD.com (0)
- PubChem (0)
- DrugBank.ca (0)
- Cafepharma (0)
- Pharmapro.com (0)

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.