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.

NE3107 (also known as HE3286)

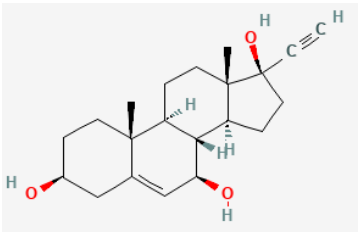
Evidence Summary

Some benefits are seen in biomarkers of people with insulin resistance and high inflammation, but these depended on several factors. Clinical trials in Alzheimer's and Parkinson's disease are ongoing.

Neuroprotective Benefit: Targeting proinflammatory signaling and insulin resistance would likely show neuroprotective benefit, but evidence is lacking in models of AD or cognitive aging. A phase 3 trial in mild-to-moderate AD is currently ongoing.

Aging and related health concerns: Small clinical studies have shown improvements in biomarkers of people with insulin resistance and high inflammation. Benefits are also seen in preclinical models of rheumatoid arthritis, glaucoma, and optic neuritis.

Safety: A few clinical trials have shown that NE3107 is generally well-tolerated, though some adverse events have occurred (e.g., increased blood amylase). NE3107 does not appear to alter levels of DHEA, testosterone, estradiol, progesterone, or cortisol.

Availability: in clinical development	**Dose**: The two ongoing trials, one in Alzheimer's and the other in Parkinson's patients, are testing an oral dose of 20 mg NE3107, twice daily (NCT04669028; NCT05083260).	**Chemical formula:** $C_{21}H_{30}O_3$ **MW**: 330.5  Source: PubChem
Company: BioVie Inc.		
Half-life: Terminal half-life of elimination is approximately 6-9 hours.	**BBB**: penetrant	
Clinical trials: There are two ongoing trials, one in Alzheimer's, and the other in Parkinson's.	**Observational studies**: None on NE3107. Plasma β-AET levels decrease with age and positively correlate with BMI (Malik et al., 2010; Auci et al., 2011).	

What is it? NE3107 (17α-ethynyl-androst-5-ene-3β,7β,17β-triol, formerly known as HE3286) is an orally administered, blood-brain barrier permeable small molecule with anti-inflammatory and insulin-sensitizing actions. It is a chemical derivative of the natural mammalian sterol androst-5-ene-3β,7β,17β-triol (βAET). βAET is a metabolite of dehydroepiandrosterone (DHEA). NE3107 binds to the extracellular signal-regulated kinase (ERK) and selectively inhibits inflammation-driven ERK- and NFκB-induced inflammatory mediators, including TNF-α, without inhibiting their homeostatic functions (Reading et al., 2021). Despite its structural similarity to DHEA and βAET, NE3107 does not exert effects on nuclear steroid hormone receptors (Reading et al., 2013). Binding partners of NE3107 include low density lipoprotein receptor-related protein (Lrp1), protein kinases involved in inflammation signaling pathways (MAPK1 and 3), an intracellular regulatory protein (Rsp6ka3), sirtuin-2, and 17β-hydroxysteroid dehydrogenase 1 (Hsd17β4), a sterol metabolizing enzyme (Reading et al., 2012).

NE3107 is currently under clinical development by BioVie Inc for the treatment of Alzheimer's disease, Parkinson's disease, multiple myeloma, and prostate cancer. In June 2021, BioVie Inc. acquired the biopharmaceutical assets of NeurMedix, Inc., a privately held clinical-stage company; the assets included NE3107 (formerly known as HE3286)(GlobalNewswire). The clinical trials testing NE3107 (HE3286) for diabetes, obesity, rheumatoid arthritis, and ulcerative colitis that took place between 2008 to 2011 were sponsored by Harbor Therapeutics (ClinicalTrials.gov).

Neuroprotective Benefit: Targeting proinflammatory signaling and insulin resistance would likely show neuroprotective benefit, but evidence is lacking in models of AD or cognitive aging. A phase 3 trial in mild-to-moderate AD is currently ongoing.

Types of evidence:

- A few laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:
None available.

Human research to suggest benefits to patients with dementia:
None available. A phase 3 study of NE3107 is currently ongoing in patients with mild-to-moderate Alzheimer's disease (NCT04669028). This double-blind, randomized, placebo-controlled trial will test an NE3107 dose of 20 mg twice daily for 30 weeks. The primary outcome measures are change from baseline in cognitive function (ADAS-Cog12) and change in function (ADCS-CGIC). The estimated study completion is in January 2023.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
NE3107 may exert neuroprotective effects through its anti-inflammatory and insulin-sensitizing activities (Reading et al., 2021). There is also ample evidence that type 2 diabetes and Alzheimer's disease share certain characteristics, including impaired insulin signaling and oxidative stress (Sebastiao et al., 2014). Thus, addressing brain insulin resistance, theoretically, is likely to show neuroprotection and cognitive benefits in Alzheimer's disease as well as in age-related cognitive decline. NE3107 has not been examined in models of Alzheimer's disease or cognitive aging, but it has reduced inflammation and activated microglia in models of optic neuritis and glaucoma (Khan et al., 2014; Lambert et al., 2017)(see details in "Aging and related health concerns").

In a mouse model of Parkinson's disease (MPTP model), treatment with NE3107 (40 mg/kg, oral gavage, BID) started 1 hour after the final MPTP and continued for 4 days significantly improved motor function (the rotarod test) compared to the vehicle group (Nicoletti et al., 2012). The treatment also reduced proinflammatory biomarkers in the brain (iNOS by 20%, p=0.002; TNF-α by 40%, p=0.038, and IL-1β by 33%, p=0.02), increased the numbers of dopaminergic (TH-positive) neurons by 17% compared to vehicle (p=0.003), and decreased the numbers of damaged neurons by 38% relative to vehicle (p=0.029).

APOE4 interactions: Unknown.

Aging and related health concerns: Small clinical studies have shown improvements in biomarkers of people with insulin resistance and high inflammation. Benefits are also seen in preclinical models of rheumatoid arthritis, glaucoma, and optic neuritis.

Types of evidence:

- 2 clinical trials
- 2 observational studies of plasma β-AET levels
- Numerous laboratory studies

Diabetes: DECREASED INSULIN RESISTANCE IN PEOPLE WITH HIGH INFLAMMATION
In a phase II trial in type 2 diabetes subjects, NE3107 (5 mg BID) as a monotherapy or in combination with metformin for 12 weeks decreased insulin resistance and improved postprandial glucose (1,5-anhydroglucitol)(Reading et al., 2013). Effects were different depending on whether patients were treatment naïve or had been treated with metformin previously, and also whether inflammation was present at baseline (measured by serum MCP-1). In metformin-treated patients, significant NE3107 treatment effects were observed in subjects with high inflammation (baseline serum MCP-1 in the upper 2 tertiles; >40 pmol/L). In these subjects, NE3107 treatment reduced HbA1c (p=0.03), HOMA2-IR (p=0.02), C-peptide (p=0.04), hemoglobin (p=0.02), hematocrit (p=0.02), and red blood cells (p=0.02) compared to those taking metformin alone. In treatment-naïve subjects, the effects of NE3107 on HbA1c were not significant, possibly due to higher variances in biomarkers compared to those of metformin-treated patients.

Overall, in metformin-treated type 2 diabetes patients, NE3107-responsive population was found in the upper two tertiles of the inflammation marker MCP-1 (>40 pmol/L). In treatment-naïve type 2 diabetes patients, the NE3107-responsive population was found in people with higher than median BMI (BMI over 31 kg/m^2). Thus, NE3107 appears to be targeting the impairment in the insulin receptor signaling pathway that is causing the chronic low-grade inflammation. People with type 2 diabetes without the chronic low-grade inflammation are likely to have glucose intolerance due to disruptions in pathways other than the insulin receptor signaling, and therefore, are not responsive to NE3107 treatment.

Several studies have tested NE3107 in animal models of diabetes. In a rat model of diabetes (Zucker diabetic fatty rats), NE3107 treatment (100 mg/kg/day) downregulated inflammatory

cytokine/chemokine expression in the liver and adipose tissue while normalizing fasting and non-fasting glucose levels, improving glucose tolerance, and enhancing insulin sensitivity in the skeletal muscle and liver (Lu et al., 2010). The treatment also decreased total serum cholesterol. In several models of diabetes (db/db mice, insulin-resistant diet-induced obese C57BL/6J mice, and ob/ob mice), treatment with NE3107 suppressed progression to hyperglycemia, markedly improved glucose clearance by reducing insulin resistance, and suppressed the adipose tissue expression of the chemokine MCP-1 (Wang et al., 2010). In mouse macrophages, exposure to NE3107 caused partial suppression of endotoxin (LPS)-induced NFkB-sensitive reporter gene expression, NFkB nuclear translocation, and NFkB/p65 serine phosphorylation. Proinflammatory kinases, including IkB kinase, JNK, and p38 MAPK, were also inhibited by NE3107.

Obesity: IMPROVED BIOMARKERS IN INSULIN-RESISTANT SUBJECTS
In a phase I study of obese subjects with impaired glucose tolerance, NE3107 treatment (2, 5 and 10 mg, twice daily) for 28 consecutive days significantly increased insulin-stimulated glucose disposal and HDL cholesterol while decreasing CRP compared to placebo (Reading et al., 2013). In insulin-resistant individuals, adiponectin levels were significantly increased, though this effect was not observed in people who were insulin-sensitive at baseline. Adiponectin can sensitize the insulin signaling pathway and suppress inflammation. There were no significant treatment effects on cholesterol, LDL, triglycerides, or bodyweight changes. NE3107 treatment did not have significant benefits in subjects who were insulin-sensitive at baseline, even with the high BMI and impaired glucose tolerance, suggesting that the treatment corrects chronic, low-grade inflammation (which may not be observed in insulin-sensitive obese individuals with impaired glucose tolerance).

NE3107 is a chemical derivative of the natural mammalian sterol, βAET, which is a metabolite of DHEA. In a study in 252 healthy men and women, plasma levels of β-AET positively correlated with body mass index (BMI)(Auci et al., 2011). The concentration of β-AET in plasma ranged from 2 to 162 pg/ml in males and from 6 to 249 pg/ml in females. In a related observational study in men and women, levels of plasma β-AET appeared to decrease with age (Malik et al., 2010). The authors of these studies suggest a compensatory increase of β-AET in people with high BMI as a mechanism to prevent the development of metabolic syndrome (Auci et al., 2011).

Rheumatoid arthritis: BENEFIT IN RODENT MODELS
A phase I/II trial testing NE3107 in rheumatoid arthritis patients has been completed (NCT00712114), but details of the trial results have not been published in a peer-reviewed article.

Several studies have also tested NE3107 in rodent models of arthritis. In a rat model of adjuvant-induced arthritis and in a mouse model of collagen antibody-induced arthritis, NE3107 treatment (ranging from 1-80 mg/kg, oral gavage) positively influenced the course of arthritis by reducing disease scores, edema, MPO activity (involved in oxidative stress and inflammation), and blood levels of inflammation biomarkers, IL-6 and TNF-α (Auci et al., 2010). NE3107 treatment was not immune-suppressive in animals challenged with the Coxsackie B3 virus. In a mouse model of collagen-induced arthritis, NE3107 treatment (40 mg/kg/day, oral gavage) started at the onset of disease significantly decreased disease (Offner et al., 2009). There was reduced joint inflammation, erosion, and synovial proliferation as measured by histological analysis and proinflammatory cytokines, including TNF-α, IL-6, IL-1β, and IL-23. When treatment was delayed until 7 days after the onset of arthritis, significant benefit was also observed. In the peak of disease and at the end of the study, there was dose-dependent benefit of NE3107 (20, 40, or 80 mg/kg/day, i.p.) in decreasing disease and inflammation biomarkers (IL-6 and MMP-3 mRNA levels) in the joints, without suppressing the immune system. These finding corroborate an older study by the same group using the same mouse model (DBA mouse model of collage-induced arthritis), where they found that NE3107 treatment (50 mg/kg/day, oral gavage) from disease onset to day 49 significantly decreased peak and daily severity of arthritis scores (Auci et al., 2007). Benefit was associated with decreased production of TNF-α, IL-6, and IL-17, decreased joint inflammation, erosion, and synovial proliferation.

Immune senescence: UNKNOWN.
NE3107 is a chemical derivative of the natural mammalian sterol, βAET. Preclinical pharmacokinetic and toxicology studies of βAET showed that a single subcutaneous administration of βAET given together with a vaccine resulted in significantly higher IgG titers than in rats receiving the vaccine alone (Ahlem et al., 2011). βAET significantly attenuated acute inflammation both *in vitro* and *in vivo*, augmented immune responses in adult mice, and reversed immune senescence in aged mice. βAET may contribute to the anti-inflammatory activity in rodents attributed to DHEA.

Glaucoma: BENEFIT IN A RODENT MODEL
Glaucoma is an age-related optic neuropathy that is sensitive to intraocular pressure. Early progression in glaucoma involves dysfunction of the optic nerve comprised by retinal ganglion cell axons. In a rat model of glaucoma (microbead occlusion), NE3107 treatment (20 or 100 mg/kg/day, oral gavage) for 4 weeks did not change intraocular pressure but preserved anterograde axonal transport from the retina while increasing the neurotrophic factor BDNF in the optic nerve head and retina (Lambert et al., 2017). Treatment with NE3107 also increased nuclear localization of NFκB in retinal neurons and decreased NFκB localization to glial nuclei in the optic nerve head.

Optic neuritis: BENEFIT IN A RODENT MODEL

Optic neuritis is characterized by optic nerve inflammation, demyelination, and axonal loss. In a mouse model of optic neuritis (EAE model), NE3107 treatment (40 mg/kg/day, i.p.) started 24 hours post-EAE and continued for 40 days reduced the level of vision loss (Khan et al., 2014). NE3107 also attenuated the degree of inflammation, demyelination, and axonal loss in the optic nerves as compared to vehicle treatment. NE3107 treatment also reduced the loss of retinal ganglion cells in the temporal retinal quadrant.

Safety: A few clinical trials have shown that NE3107 is generally well-tolerated, though some adverse events have occurred (e.g., increased blood amylase). NE3107 does not appear to alter levels of DHEA, testosterone, estradiol, progesterone, or cortisol.

Types of evidence:

- 2 clinical trials
- Several laboratory studies

Clinical trial results: Based on results from phase I/II clinical trials, NE3107 has generally been well tolerated (Reading et al., 2021). There have been no significant trends in adverse events between NE3107 and placebo groups or among dose escalation cohorts. In general the adverse events have been mild-to-moderate in nature with a majority of these events limited to abnormal laboratory values (e.g., lipase and amylase). To date, there have been three phase I, two phase I/II, and one phase II clinical trials (Reading et al., 2021). The clinical trials with published results are discussed below.

In a phase I study of activity and pharmacokinetics in obese subjects with impaired glucose tolerance, NE3107 was administered for 28 consecutive days (2, 5 and 10 mg, twice daily)(Reading et al., 2013). Of the 48 people randomized to the study, 46 people (96%) completed the study. Two subjects withdrew consent for personal reasons unrelated to the study drug. There were no significant differences between the placebo and NE3107-treated groups with regards to incidences of specific adverse events. There was also no increase in adverse events with dose escalation.

In a phase II trial in type 2 diabetes subjects, NE3107 (5 mg BID) as a monotherapy or in combination with metformin was administered for 12 weeks (Reading et al., 2013). NE3107 was well tolerated and 76% of those co-treated with metformin and 77% of those who were treatment-naïve completed the study. One serious adverse event occurred, which was a transient asymptomatic elevation from baseline

of blood amylase, which resolved during the study. This event was considered by the investigator to be possibly related to NE3107. There were no clinically significant abnormalities found in other tests or biomarkers, including hypoglycemia and electrocardiograms, that were attributable to NE3107 administration. There were no significant differences or trends in adverse events between placebo- and NE3107-treated subjects.

In addition to the studies above in diabetes and obesity, a phase I/II trial in ulcerative colitis patients and a phase I/II trial in rheumatoid arthritis patients have been completed (NCT00628433; NCT00712114).

NE3107 did not alter the concentrations of DHEA, testosterone, estradiol, progesterone, androstenedione, lutenizing hormone, follicle stimulating hormone, or adrenocorticotrophic hormone and did not affect 24-h urinary free cortisol in nonclinical safety studies or clinical trials (Reading et al., 2013).

Preclinical studies: In a mouse model of collage-induced arthritis, NE3107 was not found to be immune-suppressive in models of mitogen-induced proliferation, delayed-type hypersensitivity, and in human mixed lymphocyte response studies (Auci et al., 2007; Auci et al., 2010).

βAET: NE3107 is a chemical derivative of the natural mammalian sterol, βAET. Preclinical pharmacokinetic and toxicology studies of βAET were carried out in rats, monkeys, and cell culture (Ahlem et al., 2011). In monkeys, there was no evidence of systemic toxicity with βAET treatment (0, 42.5, 85, or 170 mg daily, s.c.) for 28 days, based on clinical pathology or histopathology, although drug administration produced dose-dependent injection site irritation. In rats, there were also no mortalities or toxicologically significant changes in clinical pathology with βAET treatment (0, 25, 50, or 100 mg/kg/day, s.c.) for 28 days. Injection site erythema was observed in all βAET-treated rats. βAET increased the absolute and relative liver weights of all animals and was associated with minimal diffuse hepatocellular hypertrophy, but not peroxisome proliferation. All findings were generally resolved by the end of the 14-day recovery period. βAET was weakly androgenic and estrogenic in immature rodents. For example, in young, castrated mice, βAET treatment at a high dose (200 mg/kg) resulted in an increase in seminal vesicle weight by 22% without a significant increase in prostate weight. In ovariectomized rats, βAET treatment increased uterine weight by 67%. βAET weakly transactivated the androgen receptor (EC50=8,200 nM), estrogen receptor α (ERα; EC50=6,500 ± 3,000 nM), and ERβ (EC50=400 nM). The glucocorticoid receptor and PPARα/γ/δ were not bound or transactivated at the highest concentration assayed (10,000 nM). βAET was not genotoxic in the Ames test, chromosome aberration test, or bone marrow micronucleus test.

Ongoing studies: In the ongoing phase 3 study testing NE3107 in mild-to-moderate Alzheimer's patients, safety will be monitored by physical examinations, 12-lead electrocardiograms, hematology, blood, and urine clinical chemistries (NCT04669028; Reading et al., 2021). In a subset of 100 patients, 24-hour urinary free cortisol will be measured. Potential estrogenic effects will be monitored with vaginal maturation index testing in a subset of 50 women.

Drug interactions: Drug interactions have not been documented. In a phase I/II trial in rheumatoid arthritis patients, NE3107 (5, 10 and 20 mg BID) treatment and the potential for drug interaction with methotrexate were evaluated for 28 days (Reading et al., 2021), but the results of this study have not been published in a peer-reviewed article. Based on the mechanism of action of NE3107, it may interact with anti-diabetes medications as well as those targeting inflammation (e.g., TNF-α inhibitors).

Sources and dosing: NE3107 is under clinical development by BioVie Inc for the treatment of Alzheimer's disease, Parkinson's disease, multiple myeloma, and prostate cancer. The two ongoing trials, one in Alzheimer's and the other in Parkinson's patients, are testing a dose of 20 mg NE3107, twice daily (NCT04669028; NCT05083260). Subjects undergo dose titration of 5 mg BID for weeks 1 and 2, 10 mg BID for weeks 3 and 4, and 20 mg BID for weeks 5-30 (Reading et al., 2021).

Research underway: There are currently two ongoing clinical trials testing NE3107. A phase 3 study of NE3107 is recruiting 316 participants with mild to moderate Alzheimer's disease (NCT04669028). This double-blind, randomized, placebo-controlled trial will test an NE3107 dose of 20 mg twice daily for 30 weeks. The primary outcome measures are change from baseline in cognitive function (ADAS-Cog12) and change in function (ADCS-CGIC). The estimated study completion is in January 2023. The other ongoing study is a phase 2a double-blind randomized placebo-controlled study of NE3107 (20 mg twice daily) in 40 participants with Parkinson's disease (NCT05083260). This study will test the safety, potential drug-drug interactions (levodopa/carbidopa), pharmacokinetics, and changes in motor function (MDS-UPDRS) in the patients. The estimated study completion is in August 2022.

Search terms:
Pubmed, Google: NE3107, HE3286

Websites visited for NE3107, HE3286:

- Clinicaltrials.gov (2)
- NIH RePORTER (0)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com (1)
- WebMD.com (0)
- PubChem
- DrugBank.ca
- Cafepharma (0)
- Pharmapro.com (0)