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 (HE3286)

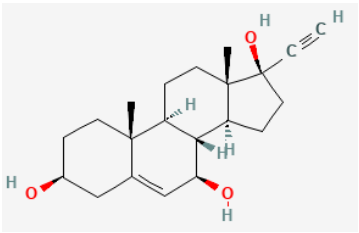
Evidence Summary

NE3107 treatment did not significantly improve cognitive and functional scores in AD patients in a phase 3 study that was underpowered; only a subset of patients' data could be analyzed due to data anomalies.

Neuroprotective Benefit: NE3107 numerically improved cognitive and functional scores in AD patients in a phase 3 clinical trial, but results were not statistically significant as only ~20% of phase 3 trial data could be analyzed due to data/site anomalies.

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: NE3107 is generally well-tolerated, but some adverse events have occurred including increased blood amylase and headache. Long-term safety beyond 6 months is unknown. NE3107 has not caused hypoglycemia, ARIA, or changes in hormone levels.

Availability: in clinical development	**Dose**: The phase 3 Alzheimer's trial tested an oral dose of 20 mg NE3107, twice daily, titrated from 5 mg twice daily for the first 2 weeks, followed by 10 mg twice daily for the following 2 weeks (NCT04669028).	**Chemical formula:** $C_{21}H_{30}O_3$ **MW**: 330.5  Source: PubChem
Half-life: Terminal half-life of elimination is approximately 6-9 hours.	**BBB**: penetrant	
Clinical trials: The largest study of NE3107 to date is the phase 3 trial in Alzheimer's patients that enrolled 439 participants.	**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 ERK1/2, which are kinases involved in inflammatory signaling and insulin responses (Reading et al., 2021). NE3107 selectively inhibits inflammation-driven ERK- and NFκB-induced inflammatory mediators, including TNF-α, without inhibiting their homeostatic functions (e.g., insulin signaling, neuronal growth/survival). Despite its structural similarity to DHEA and βAET, NE3107 does not interact with 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 for the treatment of Alzheimer's disease and Parkinson's disease by BioVie Inc. 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: NE3107 numerically improved cognitive and functional scores in AD patients in a phase 3 clinical trial, but results were not statistically significant as only ~20% of phase 3 trial data could be analyzed due to data/site anomalies.

Types of evidence:

- A phase 3 double-blind randomized controlled trial in Alzheimer's patients
- A phase 2 randomized controlled trial in Parkinson's patients
- A phase 2 open-label study in people with mild cognitive impairment and Alzheimer's disease
- 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:

Alzheimer's disease: In a phase 2, open-label, single arm trial of patients with mild cognitive impairment (MCI; n=18) or mild Alzheimer's disease (n=5), treatment with NE3107 (20 mg, twice daily, orally) for 3 months resulted in enhanced cognition compared to baseline (BioSpace article, Dec 5, 2022; AlzForum, Jan 2, 2023). However, due to the study's open-label design, it is not possible to rule out placebo effects. Participants were enrolled based on a primary complaint of memory impairment and at least one abnormal brain imaging result. The study measured changes in cognition through verbal and visual test procedures, changes in CSF and serum biomarkers of Alzheimer's disease and inflammation, and changes in MRI modalities (measuring brain glutathione levels, dendritic density, functional connectivity, and neurovascular coupling). Among MCI and mild Alzheimer's disease patients, treatment for 3 months led to a 2.1-point improvement on the modified ADAS-Cog12 scale compared to baseline (p=0.0173; equivalent to a 21.1% change). Among only responders, the improvement was 3.7 points compared to baseline (p=0.0003; equivalent to a 36.2% change). NE3107 treatment also led to an improvement of 0.11 on the Clinical Dementia Rating scale (CDR) compared to baseline (p=0.0416; equivalent to a 19.4% change) and an improvement of 0.07 points on Alzheimer's Disease Composite Score

(ADCOMS)(p=0.0094; equivalent to a 27.4% change). Patients improved in daily function as measured by an increase in the Global Rating of Change scale2: +2.67 (p<0.0001) as observed by clinicians; +2.08 (p=0.0012) as reported by the patients; and +1.69 (p=0.0011) as reported by study partners. With regards to biomarkers, NE3107 treatment reduced CSF p-tau levels by -1.66 pg/mL (p=0.0343) and the ratio of p-tau to Aβ42 by -0.0024 (p=0.0401). Among responders, the reduction in p-tau was -3.22 pg/mL (p=0.0027). Reduction in inflammation (measured by TNFα) correlated with improvements in cognition (R=0.59, p=0.0259). Out of 22 patients, 18 patients with abnormal baseline brain scans showed improvement in one or more brain regions based on functional MRI studies. MCI and mild Alzheimer's subjects with abnormal scans that improved after 3 months of NE3107 treatment also experienced a -0.068-point improvement in their ADCOMS scores (p=0.0258). MRI studies showed that with NE3107 treatment, cerebral perfusion was normalized, and functional connectivity was increased in networks involving the nucleus basalis of Meynert, the precuneus, and the hippocampus. NE3107 treatment also increased brain glutathione levels, suggesting a reduction of oxidative stress.

In December 2022, BioVie announced additional findings from this phase 2 trial through a press release (Bloomberg, Dec 6, 2022). NE3107 treatment for 3 months resulted in a reduction of 3.3 years on the Horvath DNA methylation SkinBlood epigenetic clock compared to baseline (p=0.0021). Of the 22 patients, 19 showed a reduction in the SkinBlood clock, suggesting younger "biological age" after treatment. This finding that NE3107 affected DNA methylation is consistent with NE3107's mechanism of modulating TNF, the master regulator of inflammation, which is associated with DNA hypermethylation (Stenvinkel et al., 2007).

In November 2023, BioVie announced topline efficacy results from a phase 3 study of NE3107 in patients with mild-to-moderate Alzheimer's disease (NCT04669028; BioVie press release, Nov 29, 2023). This was a double-blind, randomized, placebo-controlled trial testing oral NE3107 treatment (5 mg twice daily for weeks 1-2, 10 mg twice daily for weeks 3-4, and 20 mg twice daily for weeks 5-30) against placebo. The study enrolled a total of 439 participants across 39 clinical trial sites. However, upon trial completion, BioVie found significant deviation from protocol and Good Clinical Practice (GCP) violations at 15 sites, all of which were from one geographic area. BioVie retained three independent biostatistical consulting firms to analyze the data, and they found that several sites had inconsistent data patterns compared to historical data, with large proportions of patients improving compared to baseline, and data patterns not explainable based on established disease progression. Specifically, a prespecified demographic subgroup analysis showed that patients receiving placebo significantly improved cognitively, which cannot be explained scientifically. There were also missing data, suspected copied/pasted MRI results,

and other anomalies. BioVie then retained two new contract research organizations to conduct quality control visits at all sites and to perform source data verification at the sites.

BioVie excluded all patients from the 15 trial sites and referred these sites to the US FDA Office of Scientific Investigations. After excluding data from the 15 sites, 358 out of the total 439 participants were excluded, and only 81 patients remained in the Modified-Intent-To-Treat population, of whom 57 patients were in the Per-Protocol population and completed the trial. Of the 57 remaining participants, 24 received NE3107 treatment and 33 received placebo. The original study was designed to be 80% powered with 125 patients in each of the NE3107 and placebo groups.

The original primary outcome measures were change from baseline in cognitive function (ADAS-Cog12) and change in function (ADCS-CGIC). After amendment of the study protocol based on discussions with the FDA, the primary endpoints were finalized to be Clinical Dementia Rating scale Sum of Boxes (CDR-SB) and ADAS-Cog12. Secondary endpoints include the composite score ADCOMS, activities of daily living scale (ADCS-ADL), cognitive score (MMSE), change in function (ADCS-CGIC), neuropsychiatric index 12, and CDR global score. BioVie is working with the FDA to potentially employ an adaptive design to the trial to allow continuation of enrolling additional patients after exclusion of a large number of patients from the affected sites that made the study underpowered.

Patients treated with NE3107 for 30 weeks showed numerically better scores compared to placebo for two of the primary outcomes (CDR-SB, ADAS-Cog12), as well as four of the secondary outcomes (MMSE, ADCS-ADL, ADCS-CGIC, and ADCOMS), though none of these differences were statistically significant due to the study samples being significantly smaller than the planned study (n=23-27 for placebo group; n=24 for NE3107 group). For example, CDR-SB change from baseline was +0.44 for the NE3107 group compared to +1.39 for the placebo group (lower scores are better), and the difference between groups was -0.95 (p=0.2278). ADAS-Cog12 change from baseline was +2.70 for the NE3107 group versus +3.64 for the placebo group (lower scores are better), and the difference between groups was -0.94 (p=0.7212).

NE3107-treated patients also experienced a 4.66-year advantage in deceleration of aging compared to placebo as measured by the Horvath DNA methylation SkinBlood epigenetic clock (-7.29 years with NE3107 [n=12]; -2.63 years with placebo [n=11]; p=0.020)(BioVie press release, Nov 29, 2023).

Parkinson's disease: In a double-blind, placebo-controlled phase 2 study in 45 Parkinson's disease patients, NE3107 treatment (20 mg, twice daily, orally) with levodopa for 28 days resulted in an

improvement in motor score (Unified Parkinson's Disease Rating Scale [UPDRS] Part 3) that was 3 points superior to patients treated with levodopa alone at the 2- and 3-hour marks (BioSpace article, Dec 5, 2022; GlobeNewsWire article, Dec 5, 2022; NCT05083260). This score difference is considered to be clinically meaningful. Patients under 70 years old (roughly half of the participants) who were treated with NE3107/levodopa experienced around 6 points superiority compared to those treated with levodopa alone, suggesting that younger patients with less advanced disease progression may experience greater benefit from treatment with NE3107.

Of patients under 70 years old, 88.9% who were treated with NE3107 and levodopa experienced greater than 30% UPDRS Part 3 score improvements from baseline at the 2-hour mark compared to 63.6% of patients treated with levodopa alone.

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").

Based on media publications, NE3107 administration in marmoset monkeys was shown to be as pro-motoric as levodopa, and when NE3107 was administered with levodopa, the combination improved motor control better than either drug alone (BioSpace article, Dec 5, 2022). Additionally, NE3107 treatment reduced the severity of levodopa-induced dyskinesia concurrent with motor function benefit and decreased neurodegeneration, preserving twice as many dopaminergic neurons compared to control.

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 findings 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: NE3107 is generally well-tolerated, but some adverse events have occurred including increased blood amylase and headache. Long-term safety beyond 6 months is unknown. NE3107 has not caused hypoglycemia, ARIA, or changes in hormone levels.

Types of evidence:

- 5 clinical trials (one in type 2 diabetes, one in ulcerative colitis, 2 in Alzheimer's disease, and one in Parkinson's disease)
- 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).

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).

Results from the double-blind randomized controlled phase 2 trial in Parkinson's disease and the open-label phase 2 study in mild cognitive impairment and Alzheimer's disease have not been published in peer-reviewed papers. Based on media articles, there were no drug-related adverse events in the phase 2 Parkinson's disease trial, and no drug-related adverse events were observed in the open-label Alzheimer's trial (BioSpace article, Dec 5, 2022).

Results from the phase 3 trial in Alzheimer's patients have also not been published in peer-reviewed papers, as of January 2024. Based on media articles, NE3107 was "generally safe and well-tolerated with headache being the most common treatment-related side effect", occurring in 9.5% of patients (Alzheimer's News Today, Dec 1, 2023). NE3107 treatment did not result in brain swelling or bleeding (e.g., ARIA). Based on the company slide deck, the phase 3 trial had a low rate of adverse events, with only 10 subjects discontinuing due to a reported adverse event (2.3%)(BioVie slide deck from CTAD, Oct 24-27, 2023, Boston, MA). There were no cases of hypoglycemia.

Preclinical studies: In a mouse model of collagen-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.

Drug interactions: In the phase 2 trial in Parkinson's disease, one of the primary objectives was the assessment of drug-drug interactions between NE3107 and levodopa. NE3107 treatment did not lead to a detrimental impact on the concentration of levodopa, and its pharmacokinetic profile was maintained after 14 days of treatment, as measured by its mean blood concentration across time (Parkinson's News Today, Sep 5, 2023). 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 and Parkinson's disease. Clinical trials in Alzheimer's patients and Parkinson's patients tested an oral dose of 20 mg NE3107, twice daily (NCT04669028; NCT05083260). Subjects in the

Alzheimer's phase 3 trial underwent dose titration of 5 mg orally, twice daily for weeks 1 and 2, 10 mg twice daily for weeks 3 and 4, and 20 mg twice daily for weeks 5-30 (Reading et al., 2021).

Research underway: There is currently one ongoing clinical trials testing NE3107. It is testing the safety and efficacy of NE3107 treatment on improving sleep and fatigue in people with traumatic brain injury (NCT05970575). It is an open-label study with an estimated enrollment of 5 participants. Primary outcomes include safety (adverse events), Pittsburgh Sleep Quality Index, and Multidimensional Fatigue Inventory.

Search terms:
Pubmed, Google: NE3107, HE3286

Websites visited for NE3107, HE3286:

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

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