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.

LM11A-31 (LM11A-31-BHS, C-31)

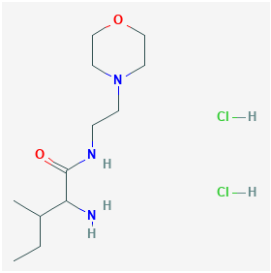
Evidence Summary

In a phase 2 study in AD patients, LM11A-31 treatment met its primary endpoint of safety. LM11A-31 did not significantly affect cognitive endpoints but improved several CSF biomarkers.

Neuroprotective Benefit: A phase 2a study reported that a 6-month treatment with LM11A-31 did not alter cognitive endpoints, but significantly decreased CSF levels of Aβ40, Aβ42, YKL-40, SNAP25, and neurogranin.

Aging and related health concerns: LM11A-31 shows some benefits in models of peripheral neuropathy, nerve injury, and retinopathy. No human clinical trials have been carried out for these conditions.

Safety: A phase 2a study in Alzheimer's patients reported that it met its primary endpoint of safety and tolerability. The most frequently observed adverse events were nasopharyngitis, diarrhea, headache, and eosinophilia.

Availability: in clinical development	**Dose**: In a phase 2 clinical trial in mild-to-moderate Alzheimer's patients, doses of 200 mg/day and 400 mg/day of LM11A-31-BHS were tested.	**Chemical formula:** $C_{12}H_{27}Cl_2N_3O_2$ **MW**: 316.26  Source: PubChem
Half life: plasma half-life of 1 hour, brain half-life of 3-4 hours in mice	**BBB**: penetrant	
Clinical trials: A phase 2 clinical trial in mild-to-moderate Alzheimer's patients enrolled 242 subjects.	**Observational studies**: none available	

What is it?

LM11A-31 is an orally available, brain-penetrant, small molecule ligand for the p75 neurotrophic receptor (p75NTR), a member of the tumor necrosis factor family of receptors whose signaling network is at the core of important resilience pathways regulating functions such as cell survival, plasticity, and synaptic integrity (reviewed in Shanks et al., 2023). Signaling of p75NTR mediates age-related decline in neuronal structure and function (Xie et al., 2019; Wang et al., 2023). In the brain, p75NTR is expressed at high levels in basal forebrain cholinergic and hippocampal pyramidal neurons, while expression is also present in the entorhinal cortex, locus coeruleus, and other regions (reviewed in Shanks et al., 2023). p75NTR binds neurotrophins such as NGF and BDNF, and its signaling can promote either neuronal survival or apoptotic death, depending on its ligand, expression patterns of other neurotrophin receptors, and downstream signaling elements. For example, proNGF induces death of neurons and oligodendrocytes through p75NTR and activation of apoptotic machinery (Lee et al., 2001; Beattie et al., 2002). In other systems, p75NTR signaling through PI3K/AKT or NFκB promotes cell survival (Carter et al., 1996; Roux et al., 2001). In neurons, p75NTR generally promotes degenerative signaling when without a ligand or when interacting with pro-neurotrophins and sortilin (Mufson et al., 2019). However, p75NTR can have trophic effects when interacting with tropomyosin receptor kinases (Trk) receptors and mature neurotrophins (reviewed in Conroy and Coulson, 2022).

p75NTR levels are increased in Alzheimer's disease and the receptor is expressed in neurons that are vulnerable to the disease (Nguyen et al., 2014). There is also an increased ratio of pro-neurotrophins to

mature neurotrophins in Alzheimer's disease, producing a shift in p75NTR signaling towards the degenerative pathway leading to synapse loss and apoptosis (Pentz et al., 2020).

LM11A-31 selectively activates p75NTR survival pathways and inhibits apoptosis signaling (Massa et al., 2006). LM11A-31 interacts with p75NTR but not TrkA.

LM11A-31-BHS, a modified version of LM11A-31 that was advanced to clinical trials, is under development by PharmatrophiX for the treatment of Alzheimer's disease.

Neuroprotective Benefit: A phase 2a study reported that a 6-month treatment with LM11A-31 did not alter cognitive endpoints, but significantly decreased CSF levels of Aβ40, Aβ42, YKL-40, SNAP25, and neurogranin.

Types of evidence:

- One phase 2a randomized controlled trial in Alzheimer's patients
- Numerous laboratory studies

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

Not available.

Human research to suggest benefits to patients with dementia:

In a phase 2a double-blind randomized placebo-controlled trial that enrolled 242 patients with mild to moderate Alzheimer's disease, the primary endpoint of safety and tolerability for LM11A-31 was met (described in detail in the "Safety" section)(Shanks et al., 2024). Patients were treated with 200 mg LM11A-31 (one capsule of 200 mg LM11A-31 and one capsule of placebo per day, orally), 400 mg LM11A-31 (two capsules of 200 mg LM11A-31 per day, orally), and placebo (2 capsules of 200 mg microcrystalline cellulose with magnesium stearate per day, orally) for 26 weeks. The trial was initiated at 21 sites located in 5 European countries: Austria, the Czech Republic, Germany, Spain, and Sweden. The 3 treatment groups did not significantly differ in key baseline variables such as age, sex, race, screening cognitive score (MMSE), screening CSF Aβ42, or use of acetylcholinesterase (AChE) inhibitors.

There was a numerically higher proportion of APOE4 carriers in the 400 mg LM11A-31 group, but the difference was not statistically significant (p=0.09).

Because longitudinal changes in CSF biomarkers, brain imaging, and cognitive tests did not differ between the 200 mg and 400 mg LM11A-31 treatment arms for 16 out of the 17 variables assessed, participants from the two LM11A-31 arms were pooled for further secondary and exploratory data analyses. Due to the exploratory trial design, statistical analyses were not corrected for multiple comparisons (Shanks et al., 2024).

Because of the short duration of treatment (26 weeks), the phase 2a trial was not powered to detect significant differences in cognitive outcomes. The secondary cognitive outcome measure, the neuropsychological test battery (NTB), at 12 and 26 weeks after treatment was not significantly different between LM11A-31 and placebo groups; the difference in median change on NTB global z-score between the LM11A-31 and placebo groups was −0.06 (95% CI, −0.14 to 0.05) at 12 weeks and −0.03 (95% CI, −0.10 to 0.04) at 26 weeks (Shanks et al., 2024). Prespecified exploratory cognitive outcomes included global scores on the Alzheimer's disease assessment scale—Cognitive subscale (ADAS-Cog-13) and the Mini-Mental State Examination (MMSE). There were no significant differences between LM11A-31 and placebo arms in longitudinal cognitive decline measured by MMSE or ADAS-Cog13 at 12 weeks or 26 weeks. For the ADAS-Cog13, the difference in median change between LM11A-31 and placebo was −1 at 12 weeks (95% CI, −3 to 1) and −1 at 26 weeks (95% CI, −2 to 2). For the MMSE, the difference in median change between LM11A-31 and placebo was 1 at 26 weeks (95% CI, −1 to 2). There were also no significant differences between treatment groups on the Clinical Global Impression score at 12 or 26 weeks (p=1.00 and 0.836, respectively). Also, no significant treatment effects were observed for spatial memory, assessed by Amunet scores (p>0.10 for all 4 Amunet memory subdomains).

Secondary CSF biomarker outcomes included changes in Aβ42, Aβ40, p-tau181, and total tau (Shanks et al., 2024). LM11A-31 treatment significantly slowed increases in CSF Aβ42 compared to placebo (Prank sum=0.037). The difference in median annual percent change of CSF Aβ42 in the LM11A-31 group relative to the placebo group was −6.98% (95% CI, −14.22 to −1.45%). LM11A-31 treatment also significantly slowed increases in CSF Aβ40 compared to placebo (Prank sum=0.009). The difference in median annual percent change of CSF Aβ40 in the LM11A-31 group relative to the placebo group was −8.96% (95% CI, −17.60 to −1.29%). There were no significant differences in treatment groups on the ratio of Aβ42/Aβ40 (Prank sum=0.952). CSF p-tau181 and total tau levels were also not significantly different between LM11A-31 and placebo groups (Prank sum=0.201 and 0.068, respectively). The difference in median annual percent change of p-tau181 between LM11A-31 and placebo groups was

−5.54% (95% CI, −12.60 to 1.17%). The difference in median annual percent change of total tau between LM11A-31 and placebo groups was −6.07% (95% CI, −17.45 to 2.71%).

Exploratory CSF biomarker outcomes included changes in synaptic markers (SNAP25, synaptotagmin 1, and neurogranin), neurodegenerative marker (neurofilament light chain; NfL), and glial biomarkers (YKL40 and soluble TREM2). LM11A-31 treatment significantly slowed increases in CSF levels of presynaptic SNAP25 compared to placebo (Prank sum=0.010)(Shanks et al., 2024). The difference in median annual percent change between LM11A-31 and placebo for CSF SNAP25 was −19.20% (95% CI, −32.19 to −1.47%). LM11A-31 treatment also significantly slowed increases in CSF levels of postsynaptic neurogranin compared to placebo (Prank sum=0.009). The difference in median annual percent change between LM11A-31 and placebo for CSF neurogranin was −9.17% (95% CI, −16.32 to −2.35%). In addition, LM11A-31 treatment significantly slowed increases in CSF YKL40 compared to placebo (Prank sum=0.040). The difference in median annual percent change between LM11A-31 and placebo for CSF YKL40 was −5.19% (95% CI, −14.80 to 2.49%). There were no significant differences between LM11A-31 and placebo groups on CSF synpatotagmin 1 levels (Prank sum=0.426), CSF NfL levels (Prank sum=0.315), or CSF soluble TREM2 levels (Prank sum=0.172).

The effects of LM11A-31 on gray matter integrity (measured by structural MRI) and brain glucose metabolism (measured by FDG-PET) were also assessed. In a voxel-wise structural MRI analysis of gray matter volume, a significant hypothesis-consistent treatment group x time interaction was observed at an uncorrected threshold of $p<0.001$ (Shanks et al., 2024). Compared to placebo, LM11A-31 treatment slowed the rate of gray matter loss in the frontal operculum and posterior parietal cortex. For brain glucose metabolism, no voxels exhibited a treatment group x time interaction effect at the uncorrected threshold of $p<0.001$. When the threshold was raised to a liberal $p<0.05$, a hypothesis-consistent treatment group-by-time interaction was detected, where LM11A-31 treatment slowed rates of glucose metabolic decline in regions such as the entorhinal cortex, hippocampus, insula, and prefrontal cortex.

Larger and longer-duration clinical trials of LM11A-31 in Alzheimer's patients are needed to determine whether LM11A-31 treatment may slow disease progression and cognitive decline.

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

Neuroprotective potential of LM11A-31 has been tested in numerous animal models. LM11A-31 crosses the blood-brain barrier based on rodent studies (Knowles et al., 2013).

Alzheimer's disease models: LM11A-31 treatment has shown neuroprotective benefits in 3 models of Alzheimer's disease.

In a mouse model of Alzheimer's disease ($APP^{L/S}$ mice), LM11A-31 treatment (0, 10, or 50 mg/kg/day, orally) for 3 months prevented deficits in novel object recognition and Y-maze performance (Knowles et al., 2013). In these mice, neuritic dystrophy was present in the basal forebrain, hippocampus, and cortex, but was significantly reduced by LM11A-31 treatment, with no effects on amyloid levels.

In the same mouse model as above ($APP^{L/S}$ mice), LM11A-31 treatment (5, 25, 50, or 100 mg/kg/day, oral gavage) for 3 months prevented cognitive impairment as measured by water maze performance and fear conditioning, reduced phosphorylation of tau, inhibited aberrant tau folding, decreased microglial activation, and attenuated reactive astrocytes (Nguyen et al., 2014). LM11A-31 treatment also decreased cholinergic neurite degeneration.

In two mouse models of Alzheimer's disease ($APP^{L/S}$ mice and Tg2576 mice), LM11A-31 treatment (50 or 75 mg/kg, oral gavage) for 3 months at age-ranges during which marked Alzheimer's-like pathology manifests prevented and/or reversed atrophy of basal forebrain cholinergic neurites and cortical dystrophic neurites (Simmons et al., 2014). In $APP^{L/S}$ mice, LM11A-31 treatment started both in mid-stage (6-8 months of age) and in late-stage pathology (12-13 months) was successful in reversing the degeneration of neurites. Similar results were seen in female Tg2576 mice.

In a mouse model of Alzheimer's disease ($APP^{L/S}$ mice), LM11A-31 treatment (50 mg/kg/day, 6 days/week) for 3 months significantly lowered microglial activation, as measured by TSPO-PET ([18F]GE-180-PET imaging)(James et al., 2017).

Also in $APP^{L/S}$ mice, LM11A-31 treatment for 3 months (from age 7.5-8 months to 10.5-11 months) rescued the significant spine density loss (~42%) such that spine density was comparable to that of vehicle-treated wild-type mice (Yang et al., 2020). In neurons exposed to oligomeric Aβ, LM11A-31 treatment inhibited Aβ-associated degeneration of neurites and spines. LM11A-31 treatment also inhibited tau phosphorylation, cleavage, oligomerization, and missorting. $APP^{L/S}$ mice has increased levels of tau cleaved at Asp421, but treatment with LM11A-31 reduced these levels, in part, through the normalization of caspase 3/7 activity to baseline levels. Increased missorting of tau and its accumulation in dendrites leads to increased Fyn binding, which in turn facilitates Fyn-mediated phosphorylation of the NMDA receptor GluN2B subunit that are associated with glutamate excitotoxicity (Um et al., 2012). In hippocampal neuron cultures, LM11A-31 treatment prevented the Aβ-induced increase in the active

form of Fyn (measured by p-FynY416), as well as Fyn kinase targets that play major roles in synaptotoxicity (p-tau-Y18 and p-GluN2B-Y1472)(Yang et al., 2020). In hippocampal neuronal cultures, Aβ oligomer exposure induced spine loss and decreased phosphorylation (Ser3) of cofilin, an actin-binding protein that plays an essential role in regulating actin dynamics and neuronal/synaptic morphology (Yang et al., 2020). However, these reductions were inhibited by administration of LM11A-31. Cofilin phosphorylation was also reduced in $APP^{L/S}$ mice, but levels were restored by treatment with LM11A-31. These actions may be through inhibition of RhoA, which is an important regulator of neurite growth and dendritic spine dynamics.

In a mouse model of tauopathy (PS19 mice), LM11A-31 treatment (50 mg/kg, oral gavage, 5 days/week) started at 6 months of age (after tau pathology onset) and continued for 3 months improved hippocampus-dependent behaviors, measured by the Morris water maze and novel object recognition test (Yang et al., 2020). Trends for improvement in fear conditioning were seen with LM11A-31 treatment, but the results were not statistically significant. Cognitive benefits with LM11A-31 were seen concurrently with reductions in 1) excess activation of hippocampal cdk5 and JNK kinases and calpain, 2) excess cofilin phosphorylation, 3) tau phosphorylation, acetylation and cleavage, 4) multiple forms of insoluble tau aggregates and filaments, and 5) microglial activation. Hippocampal extracts from treated mice had significantly reduced seed-competent tau. In pyramidal neurons, LM11A-31 treatment reversed dendritic spine loss and restored dendritic complexity. LM11A-31 did not improve cognitive performance in non-transgenic mice, suggesting that LM11A-31 does not have a non-specific cognitive enhancing effect.

Old mice: Aging is associated with degeneration of basal forebrain cholinergic neurons and cognitive impairment. In aged mice, LM11A-31 treatment (50 mg/kg/day, oral gavage) started at the age of 15-18 months resulted in a dose-related preservation of basal forebrain cholinergic neurons (Xie et al., 2019). Even a one-month treatment started at 17-18 months of age also preserved cholinergic cell area. In very old mice aged 21 to 25 months old, LM11A-21 treatment increased cell size beyond that observed in 18-month-old mice, increased neurite length, and increased cholinergic fiber density. LM11A-31 treatment also increased the number of synapses in the hippocampus, as measured by synaptophysin levels. These studies suggest that LM11A-31 may prevent and also reverse age-associated basal forebrain degeneration.

Huntington's disease model: In a mouse model of Huntington's disease (R6/2 mice), treatment with LM11A-31 (50 mg/kg/day, oral gavage, 5-6 days/week) for 7-8 weeks starting at 4 weeks of age before cognitive/motor symptom onset alleviated volume reductions in multiple brain regions, including

striatum, globus pallidus, cortex, corpus callosum and contiguous external capsule (Simmons et al., 2021). However, no treatment effects were seen in the volumes of the hippocampus or thalamus.

LM11A-31 treatment also normalized changes in diffusion tensor imaging metrics and diminished increases in plasma cytokine levels, including TNF-α, IL-1β, and IL-6. Also, R6/2 mice treated with vehicle had increased urinary levels of the p75NTR extracellular domain (ecd), a cleavage product released with pro-apoptotic ligand binding, while LM11A-31 treatment reduced this increase. While further research is needed, levels of urinary p75NTR-ecd may have the potential to be a surrogate marker of disease state and therapeutic efficacy in Huntington's disease.

HIV/FIV models: HIV can penetrate into the brain and the presence of HIV in the central nervous system leads to cognitive deficits in many people living with HIV even with antiretroviral treatment. In FIV-infected cats that were beginning to show cognitive deficits, LM11A-31 treatment (13 mg/kg, twice daily) for 10 weeks normalized the deficits, as measured by T-maze testing and novel object recognition (Fogle et al., 2021). Although LM11A-31 treatment did not affect systemic FIV titers, there was a log drop in CSF FIV titers.

In a mouse model of HIV (HIV gp120 transgenic mice), LM11A-31 treatment (50 mg/kg/day) for 4 months suppressed microglial (but not astrocytic) activation, increased microtubule associated protein-2 (MAP-2) expression, reduced dendritic varicosities, and slowed the loss of parvalbumin-positive neurons in the hippocampus (Xie et al., 2021).

In cultured rat neurons exposed to HIV gp120 or to conditioned medium from human monocyte-derived macrophages treated with gp120, LM11A-31 administration at nanomolar concentrations prevented cell death, stabilized calcium homeostasis, prevented the development of dendritic swelling (beading) and cytoskeletal damage, and restored mitochondrial movement (Meeker et al., 2016). The restorative effects of LM11A-31 may be due, in part, to the sustained activation of phospho-Akt and phospho-CREB in neurons, prevention of actin disruption, and preservation of the transport of mitochondria.

Traumatic brain injury model: In a rat model of traumatic brain injury, LM11A-31 treatment (50 or 75 mg/kg/day, i.p.) started at 24 hours after injury (controlled cortical impact) and continued for 21 days significantly improved learning and memory outcomes (Haefeli et al., 2017).

In a mouse model of repetitive mild traumatic brain injury, treatment with LM11A-31 (50 mg/kg, i.p.) one hour before the first hit and on days 0, 1, 3, and 7 resulted in better recovery of axonal integrity

(increased axonal number and length) and cognitive function, measured by the novel object recognition and Morris water maze (Liu et al., 2024).

Sepsis-induced cognitive impairment: In a mouse model of sepsis-induced cognitive impairment (induced by cecal ligation and puncture), LM11A-31 treatment (50 mg/kg/day, in drinking water) started immediately after surgery significantly reversed the sepsis-induced cognitive impairment (measured by novel object discrimination and fear conditioning) and attenuated the sepsis-induced hippocampal inflammatory responses and neuronal cell death (Ji et al., 2018). Specifically, IL-1β levels were elevated in septic mice but restored with LM11A-31 treatment. TNF-α and IL-6 levels were not altered with treatment. Sepsis increased microglial activity (measured by IBA1+ cells) and caspase-3-positive cells in the CA1, CA3, and DG of the hippocampus, but these were restored with LM11A-31 treatment. The number of spines as well as BDNF levels were significantly decreased in septic mice, but LM11A-31 treatment restored these to levels comparable to sham-operated mice.

Meningitis model: In a rat model of *Streptococcus pneumonia*e meningitis, intranasal pretreatment with LM11A-31 (15 µg/day for 3 days) alleviated clinical severity, histopathological injury, and activation of astrocytes and microglia in the cortex and hippocampus (Zhang et al., 2021). LM11A-31 pretreatment also significantly reduced neuronal apoptosis (measured by TUNEL) and necrosis (measured by FJB), and decreased the expression of inflammation-related transcription factors (NF-κBp65, C/EBPβ) and proinflammatory cytokines/mediators (IL-1β, TNF-α, IL-6 and iNOS) in the cortex and hippocampus at 24 hours post-meningitis. When intranasal LM11A-31 treatment was extended for 7 days after meningitis, there was accelerated resolution of inflammation and increased proliferation of neuronal precursor cells in the hippocampus on days 7 and 14.

APOE4 interactions: Unknown.

Aging and related health concerns: LM11A-31 shows some benefits in models of peripheral neuropathy, nerve injury, and retinopathy. No human clinical trials have been carried out for these conditions.

Types of evidence:

- Several laboratory studies

No clinical trials have tested LM11A-31 in patients with age-related health conditions. Several studies have tested LM11A-31 in animal and cell culture models of age-related diseases.

Mortality: EXTENDED LIFESPAN IN A MOUSE MODEL OF TAUOPATHY
In the PS19 mouse model of tauopathy, survival rate is 64% at the 9-month time point while rates for non-transgenic mice were 97-100% (Yang et al., 2020). LM11A-31 treatment (50 mg/kg, oral gavage, 5 days/week) started at 6 months of age (after tau pathology onset) and continued for 3 months significantly improved survival rate to 94% at 9 months. In a separate survival study, 50% of PS19 mice treated with vehicle reached 327 days old, whereas 50% of PS19 mice treated with LM11A-31 reached 404 days old. Treatment with LM11A-31 extended survival in PS19 mice with an increase in median survival time from 334 to 443 days (33% increase)(p=0.0032).

Peripheral neuropathy, nerve injury: BENEFIT IN RODENT MODELS
In a mouse model of peripheral neuropathy (cisplatin-induced experimental peripheral neuropathy), treatment with LM11A-31 (25 or 50 mg/kg, i.p., once daily) for 10 weeks prevented the decrease in peripheral nerve sensation, while alleviating cisplatin-induced abnormal sural nerve fiber morphology (Friesland et al., 2014). Rho GTPase activation is increased following trauma in several models of neuronal injury and cisplatin-treated mice also had increased RhoA activity (increased p-RhoA), while this effect was reversed by LM11A-31 treatment.

In a mouse model of peripheral nerve injury (induced by sciatic nerve transection), LM11A-31 applied to the site of injury resulted in successful regeneration of axons of nearly three times as many motoneurons and reinnervation of twice as many muscle fibers by regenerating motor axons (15.6% vs 8.4%), compared to untreated controls (McGregor et al., 2021). LM11A-31 treatment to the injured nerve stump also enhanced functional recovery, as measured through motor unit number estimation (MUNE; 43.1 vs 15.2 in untreated mice). Expression of p75NTR surrounding regenerating axons appears to contribute to poor regeneration during the first two weeks after peripheral nerve injury, during which LM11A-31 treatment was beneficial.

In mice with unilateral sciatic denervation, LM11A-31 treatment (75 mg/kg/day) for 1 week significantly reduced JNK activation and attenuated the upregulation of proinflammatory cytokines (IL-6 and TGF-β) in the denervated muscle (Aby et al., 2021). However, upregulation of another proinflammatory cytokine, IL-1β, was unaffected in the denervated muscle. There were also no significant effects of LM11A-31 treatment on macrophage infiltration in the denervated muscle or denervation-induced muscle atrophy.

In a mouse model of spinal contusion injury, LM11A-31 treatment (0, 10, 25, or 100 mg/kg, oral gavage, twice daily) beginning 4 hours after injury and until study completion promoted functional recovery and survival of oligodendrocytes while increasing the number of myelinated axons by twofold at the highest dose (Tep et al., 2013). LM11A-31 was effective in improving motor function and coordination, as measured by both weight-bearing open-field tests and non-weight-bearing swim tests. The functional improvement correlated with an over 50% increase in the number of surviving oligodendrocytes and myelinated axons. LM11A-31 inhibited proNGF binding to p75NTR, thereby preventing the JNK3-mediated apoptotic signaling. It is not known whether a further delay in LM11A-31 treatment (beyond 4 hours post-injury) will show protective benefit.

In a mouse model of spinal contusion injury, LM11A-31 treatment (100 mg/kg, oral gavage) the first 7 days after injury reduced cell death in the spinal cord (Ikeda et al., 2022). Nerve fiber tracks were spared, measured by MRI and diffusion tensor imaging.

Spinal cord injuries also affect physical mobility and impairs the function of organs, leading to lower urinary tract dysfunctions manifesting as detrusor sphincter dyssynergia and neurogenic detrusor overactivity. In a mouse model of spinal cord injury-induced lower urinary tract dysfunction (detrusor sphincter dyssynergia), LM11A-31 treatment (100 mg/kg/day, oral gavage) started 7 days following injury and for up to 6 weeks ameliorated the detrusor sphincter dyssynergia and detrusor overactivity, significantly improving bladder function and preventing the urothelial damage and bladder wall remodeling (Zabbarova et al., 2018). Pretreatment with LM11A-31 (started 1 day before injury) prevented the spinal cord injury-induced morphological changes in the bladder wall.

Retinopathy: IMPROVED IN MOUSE MODELS
In a mouse model of retinal ischemia-reperfusion, LM11A-31 treatment (50 mg/kg, every other day) started 48 hours after injury significantly ameliorated visual function, as measured by the visual-clue water maze test (Elshaer et al., 2021).

Diabetic macular edema, which can lead to vision loss, can be set off by the breakdown of the inner blood-retinal barrier. Diabetes causes an imbalance of NGF isoforms such that proNGF and its receptor, p75NTR, are upregulated (Elshaer et al., 2019). In a mouse model of diabetes-induced retinal vascular permeability (induced by streptozotocin injection), LM11A-31 treatment (50 mg/kg/day, oral gavage) for 4 weeks significantly mitigated proNGF, VEGF, IL-1β, and TNF-α expression, while preserving the blood-retinal barrier integrity (Elshaer et al., 2019). The mechanism through which LM11A-31 preserves the

blood-retinal barrier integrity involves modulation of the upregulated p75NTR–RhoA kinase pathway as well as controlling the paracrine effects (e.g., VEGF) and proinflammatory mediators in the retina.

Stroke: BENEFIT IN MOUSE MODELS
In a mouse model of stroke (middle cerebral artery occlusion), treatment with LM11A-31 (50 mg/kg, oral gavage) started 1 week after stroke and continued for up to 12 weeks resulted in less brain atrophy, improved recovery of motor function (measured by the ladder test), improvement in some cognitive measures (measured by the nest construction test and open field test), less neurodegeneration, less tau pathology, less microglial activation, higher levels of neurotransmitters (serotonin, acetylcholine, and dopamine), and improved redox homeostasis (restoring reduced glutathione)(Nguyen et al., 2022). However, LM11A-31 treatment did not improve performance on the Y-maze test or the novel object recognition test. LM11A-31 treatment did not affect cytokine levels or adaptive immune cell infiltration in the infarct, suggesting that LM11A-31 does not alter chronic inflammatory responses.

In a mouse model of acute stroke injury (transient distal middle cerebral artery occlusion), LM11A-31 treatment (25 mg/kg, i.p., twice daily) for 72 hours post-injury reduced blood-brain barrier permeability, cerebral tissue injury, and sensorimotor function (Nassohi et al., 2023). In the treated mice, brain samples had less proNGF/p75NTR signaling, caspase 3 activation (apoptosis marker), reactive microglia, and IL-1β production. In the same mouse model, when LM11A-31 treatment was started after 72 hours-post-stroke and continued until day 14, no improvements in cortical atrophy or sensorimotor function were observed.

In a mouse model of ischemic stroke (middle cerebral artery occlusion), a single injection of LM11A-31 (50 mg/kg, i.p.) 1 hour post-stroke reduced infarct size, edema, and hemorrhagic transformation (Mirzahosseini et al., 2024). Additionally, protein expression of TNF-α which is elevated after stroke while treatment with LM11A-31 slightly decreased this elevation.

Arthritis: DECREASED IL-6 IN *IN VITRO* STUDIES
In patients with arthritis, high levels of NGF are observed. In synovial tissue and cells of patients with juvenile idiopathic arthritis, inflamed synoviae express high levels of proNGF and p75NTR, which correlated with the severity of clinical symptoms (Minnone et al., 2017). Notably, inhibition of p75NTR with LM11A-31 abolished the proNGF-induced production of IL-6 in patients' mononuclear cells, while inhibition of TrkA did not. These cell culture studies suggest that the proNGF-p75NTR axis promotes proinflammatory mechanisms contributing to chronic tissue inflammation, while inhibition of p75NTR

may dampen the inflammation. It is currently unknown whether these *in vitro* findings would translate to benefits in human patients with arthritis.

Safety: A phase 2a study in Alzheimer's patients reported that it met its primary endpoint of safety and tolerability. The most frequently observed adverse events were nasopharyngitis, diarrhea, headache, and eosinophilia.

Types of evidence:

- One phase 2a randomized controlled trial in Alzheimer's patients
- Several laboratory studies

In a phase 2a double-blind randomized placebo-controlled trial that enrolled 242 patients with mild to moderate Alzheimer's disease, the primary endpoint of safety and tolerability for LM11A-31 was met (Shanks et al., 2024). The most frequently observed adverse events were nasopharyngitis, diarrhea, headache and eosinophilia, and in most cases, adverse events were transient. Nasopharyngitis (17 participants) and diarrhea (13 participants) were significantly more commonly reported in the 400 mg LM11A-31 group compared to placebo (OR with 95% CI: nasopharyngitis, 5.41 [1.15 to 25.52]; diarrhea, 12.22 [1.54 to 97.00]; $p<0.05$ for both). Of these participants, 2 withdrew from the study due to diarrhea and none withdrew due to nasopharyngitis. Headache was experienced by 12 participants; 2 in the placebo group, 5 in the 200-mg LM11A-31 group and 5 in the 400-mg LM11A-31 group (2.53 [0.48 to 13.44]). There were no discontinuations due to headache. There were more discontinuations in the 400-mg LM11A-31 group (n=12) than in the 200-mg (n=3) and placebo (n=5) groups.

Eosinophilia (high levels of eosinophils) occurred in 10 participants, 5 in the 200-mg LM11A-31 group and 5 in the 400-mg LM11A-31 group (Shanks et al., 2024). Of these 10 people, 3 were removed from the study, and the study drug was discontinued temporarily in 2 participants. Eosinophil increases were asymptomatic and none were classified as serious adverse events. Four participants experienced eosinophil increases to levels greater than 500 per mm^3 above baseline, but these values resolved to within the normal range by each participant's next scheduled visit (a time range of approximately 1 month). No participants in the placebo group exhibited eosinophilia.

A total of 33 participants (14%) experienced adverse events considered to be related to the study medications (n=8 [10%] in placebo, n=12 [15%] in 200 mg LM11A-31, and n=13 [16%] in 400 mg LM11A-31 group)(Shanks et al., 2024). A total of 15 serious adverse events occurred in the study across 15

participants. Of these participants, 2 experienced a serious adverse event before dosing, 4 were in the placebo group, 2 were in the 200 mg LM11A-31 group, and 7 were in the 400 mg LM11A-31 group. One serious adverse event of gastrointestinal bleeding occurred after 16 days of dosing and was classified as possibly being related to LM11A-31 treatment. This participant withdrew from the study and was found by endoscopic exam to have a gastric ulcer of unknown duration and fully recovered.

A total of 20 participants discontinued the study medication (Shanks et al., 2024). Reasons for discontinuation were adverse events (n=2 in placebo, n=2 in 200 mg LM11A-31, and n=8 in 400 mg LM11A-31 group), serious adverse events (n=1 in placebo and n = 3 in 400 mg LM11A-31 group), and withdrawal of consent (n=2 in placebo, n=1 in 200 mg LM11A-31, and n=1 in 400 mg LM11A-31 group). The most common reason for discontinuing the study was gastrointestinal symptoms, followed by eosinophilia. One participant in the placebo group died during the trial and cause of death was pancreatic adenocarcinoma. There were no deaths in the LM11A-31 groups.

No significant abnormalities in vital signs (blood pressure, heart rate, respiratory rate and body temperature), 12-lead electrocardiogram or clinical laboratory assessment (hematology, biochemistry, coagulation, serology and urinalysis) were observed in placebo or LM11A-31 treatment arms. While no significant changes in systolic blood pressure were observed across groups, changes in diastolic blood pressure were significantly different among the 3 groups (p=0.036). The median change in diastolic blood pressure was +1 mmHg in the placebo group, 0 mmHg in the 200 mg LM11A-31 group, and −2 mmHg in the 400 mg LM11A-31 group. Post hoc testing (Dunn's test) showed that the median longitudinal change in diastolic blood pressure was statistically significantly lower in the 400 mg LM11A-31 group compared to the placebo group (p=0.010); however, the magnitude of difference in diastolic blood pressure was not clinically significant.

MRI studies did not detect concerns regarding safety, including amyloid-related imaging abnormalities (ARIAs).

In addition to the above phase 2 study, there have been two phase 1 studies testing LM11A-31-BHS in healthy subjects (PharmatrophiX). Details of the phase I trial data have not been made public.

In FIV-infected cats, treatment with LM11A-31 (10 mg free base/kg), orally, intravenously, and subcutaneously did not result in any significant adverse effects (Fogle et al., 2021). A decreased hematocrit was noted in 2 out of 4 cats at 48 hours following oral dosing, in 1 out of 2 cats at 72 hours following intravenous dosing and in 2 out of 2 cats following subcutaneous dosing. The effect was

transient, and the cats in chronic dosing study exhibited only sporadic, mild decreases in hematocrit over the entire study period. No other significant laboratory changes were noted on the CBC, serum biochemistry profile or urinalysis throughout the entire length of the study. Body weight, body condition score, sensory perception, and daily activity were not affected by LM11A-31 treatment.

In humans, intrathecal administration of NGF for the treatment of Alzheimer's was limited by severe pain (Eriksdotter Jonhagen et al., 1998). Similar symptoms including pain and weight loss have been observed in rodents after peripheral NGF treatment. In a mouse model of Alzheimer's disease ($APP^{L/S}$ mice), LM11A-31 treatment (10 or 50 mg/kg/day, oral gavage) for 3 months did not induce hyperalgesia induced by heat (Knowles et al., 2013).

In a mouse model of spinal cord injury (spinal contusion injury), LM11A-31 treatment (0, 10, 25, 100 mg/kg, oral gavage) beginning at 4 hours post-injury and continued twice daily until study completion did not cause any weight loss or other obvious adverse effects (Tep et al., 2013). Also, LM11A-31 did not exacerbate pain sensitivity.

Drug interactions: Drug interactions for LM11A-31 or LM11A-31-BHS have not been well documented.

Sources and dosing:

LM11A-31 and LM11A-31-BHS are under clinical development by PharmatrophiX. LM11A-31-BHS is a modified version of LM11A-31 that was advanced to clinical trials. In a randomized double-blind phase 2a clinical trial in mild-to-moderate Alzheimer's patients, doses of 200 mg/day and 400 mg/day of LM11A-31-BHS (200 mg capsules of LM11A-31 or placebo, taken orally, twice daily) have been tested (Shanks et al., 2024).

In rodent studies, doses ranging from 5 to 100 mg/kg have been used, with 50 mg/kg being the most common (Nguyen et al., 2014; Xie et al., 2019; Yang et al., 2020; Simmons et al., 2021). Most studies used the oral gavage route. In a study in an Alzheimer's mouse model, LM11A-31 [2-amino-3-methyl-pentanoic acid (2-morpholin-4-yl-ethyl)-amide], was custom manufactured in the hydrochloride salt form by Olon Ricerca Biosciences LLC (Concord, OH) (Yang et al., 2020). Each preparation was purified by HPLC, at greater than 99.8% purity. For *in vitro* testing, LM11A-31 was dissolved in water prior to dilution in culture medium. For *in vivo* testing, LM11A-31 was dissolved in water at a concentration of 5 mg/ml and stored at −20 °C.

Research underway:

NIH is currently funding several programs that use LM11A-31 in the context of post-stroke cognitive dysfunction, HIV-induced neurocognitive impairment, spinal cord injury, hind limb ischemia, and radiation cystitis (NIH RePORTER).

Search terms:
Pubmed, Google: LM11A-31, LM11A-31-BHS, C-31

Websites visited for LM11A-31:

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