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.

p38α MAPK Inhibitors

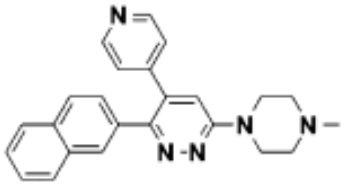
Evidence Summary

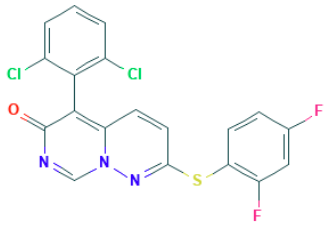
Some preliminary evidence suggests that p38α inhibitors may be useful for dementias such as AD and DLB or certain cardiovascular events. However, larger trials at higher doses are needed.

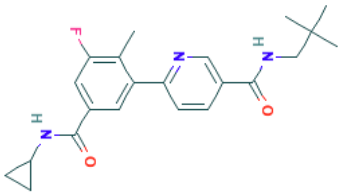
Neuroprotective Benefit: Small clinical trials have not found efficacy in AD, though this may be due to too-low dosing; patients who received higher doses may have experienced some benefit. Some potential benefit was seen in DLB populations.

Aging and related health concerns: Losmapimod may improve certain aspects of atherosclerosis, such as a reduction in plaque inflammation, though a large clinical trial suggests it may not reduce CVD events in a secondary prevention setting.

Safety: Studies suggest some risk for elevated liver enzymes, though larger trials are needed to explore this risk. Common side effects include gastrointestinal disturbances and headache, and may include somnolence.

Availability: in clinical development.	**Dose**: No currently established dose	**Chemical formula:** $C_{24}H_{23}N_5$ **MW**: 381.47g/mol; **MW150**  Source: Roy et al, 2015
Half-life: > 3 hours (animals)	**BBB**: Penetrant in animals.	
Clinical trials: MW150 has been tested in 1 phase 1 trial of 10 people.	**Observational studies**: None.	

Availability: in clinical development.	**Dose**: 40 mg bid has been tested; tid may be a preferable dose.	**Chemical formula:** $C_{19}H_9Cl_2F_2N_3OS$ **MW**: 436.258g/mol; **Neflamapimod (VX-745)**  Source: Pubchem
Half-life: Not reported.	**BBB**: Penetrant.	
Clinical trials: Neflamapimod has been tested in a few small clinical trials totaling 268 patients.	**Observational studies**: None.	

Availability: in clinical development.	**Dose**: 7.5 mg bid.	**Chemical formula:** $C_{22}H_{26}FN_3O_2$ **MW**: 383.467g/mol; **Losmapimod (GW8566553X)**  Source: Pubchem
Half-life: 7.9-9 hours	**BBB**: Unknown.	
Clinical trials: Largest study identified enrolled 3,500 patients.	**Observational studies**: None.	

What is it?

As reviewed by Canovas & Nebreda, 2021, p38 kinases are serine/threonine protein kinases in the mitogen-activated protein kinase (MAPK) family. There are four p38 kinases: p38α, p38β, p38γ, and p38δ. This report will focus on p38α. Unlike other members of the MAPK family, p38 kinases generally respond to stressors ranging from environmental stress to inflammatory signals rather than mitogens. p38 signaling is complex and context dependent, with many different upstream activators that can result in very different downstream consequences. The level of activation of p38α also matters; for instance, mild activation of p38α by lower levels of reactive oxygen species (ROS) is thought to lead to cell proliferation and differentiation, whereas stronger activation by higher levels of ROS may lead to cell death, inflammation, and neurodegeneration. As p38α plays a role in so many different aspects of cellular function in response to stress, modulating its activity has been of interest for several diseases, including inflammatory diseases, cancer, pain, and neurodegenerative disorders.

There are numerous p38 inhibitors (Hammaker & Firestein, 2011; Phan et al., 2023). The original p38 inhibitor report focused on three of the better studied p38α inhibitors: MW150, neflamapimod, and losmapimod. This update will focus on new information about MW150 and neflamapimod.

MW150 is a p38α MAPK inhibitor under development by Neurokine Therapeutics. It was invented by ADDF-funded investigator, Martin Watterson, MD, at Northwestern University, and ADDF provided funding for a phase 1 safety study. Neflamapimod is another p38α MAPK inhibitor initially developed by Vertex Pharmaceuticals for rheumatoid arthritis. After Vertex dropped the program, EIP Pharma licensed it for Alzheimer's disease (AD). Neflamapimod is currently under development for AD and dementia with Lewy bodies (DLB) and has been given fast-track designation for the latter; neflamapimod had also been developed for Huntington's disease (HD), but this indication has been discontinued. Losmapimod, a p38α and p38β MAPK inhibitor, was originally developed by GlaxoSmithKline. It failed in multiple trials of many diseases and was subsequently dropped. Losmapimod was then acquired by Fulcrum Therapeutics and is under development for a subtype of muscular dystrophy known as facioscapulohumeral muscular dystrophy, for which losmapimod has been given fast-track and orphan drug designations (Press release).

Neuroprotective Benefit: Small clinical trials have not found efficacy in AD, though this may be due to too-low dosing; patients who received higher doses may have experienced some benefit. Some potential benefit was seen in DLB populations.

Types of evidence:

- 2 randomized controlled trials
- One open-label clinical study of neflamapimod in Alzheimer's patients
- Multiple pathology studies in Alzheimer's brain tissue
- 5 reviews
- 10 laboratory studies

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

Phosphorylated-p38 (p-p38) MAPK expression was increased in the early Alzheimer's patients (Braak stages IV-V, and in some later Alzheimer's patients at Braak stage VI – note: Braak staging is a measure of how much tau has spread). It was expressed in neurons as p-tau started to be expressed, but it was no longer present in neurons with established, dense neurofibrillary tangles, suggesting its expression increases transiently. There was no correlation between p-p38 MAPK and amyloid plaques (Sun et al., 2003). However, an early study by the same group found p-p38 MAPK expression in cells near amyloid plaques and tau tangles (Hensley et al., 1999), and another study found that pMKK6, an upstream activator of p38 MAPK, is increased in the hippocampus of patients with Alzheimer's disease and is associated with plaques and tangles (Zhu et al., 2001). Another study reported an increase in p-p38 MAPK in peripheral blood lymphocytes in patients with Alzheimer's disease and that the increase correlated with disease progression and inversely correlated with cognition (Wang et al., 2014).

Human research to suggest benefits to patients with dementia:

In an open-label clinical study over 84 days with two doses of neflamapimod (40 or 125mg bid), there were no group level effects for a reduction in amyloid PET in patients with MCI or mild Alzheimer's. However, in a prespecified responder analysis (>7% reduction in amyloid PET signal), there were 3 responders (out of 9 patients) in the 40 mg group and 1 responder (out of 7 patients) in the 125 mg group. Patients had improved immediate and delayed recall compared to baseline, and this correlated with plasma drug concentrations (r^2=0.70) There were no effects on recognition memory (Sheltens et al.,

2018). In another analysis of this clinical trial, neflamapimod was reported to cross the blood brain barrier (CSF to unbound plasma ratio ~1.2) and to reduce the CSF levels of IL-8 and TNFα (Alam et al., 2017). Note that this trial was not placebo controlled.

REVERSE-SD was a randomized blinded trial of neflamapimod in patients with mild AD. The 161 participants were randomized to either 40 mg of neflamapimod or placebo orally twice daily for 24 weeks. The researchers looked at the change in cognitive performance from baseline to the end of the trial. They found no overall difference in change in cognitive function between the treated group and the placebo group over the course of the trial. Pre-specified exploratory analyses hinted at potential cognitive benefit in patients who had higher drug exposure.

The trial did detect a statistically significant decrease in CSF levels of tau and p-tau 181 in the treated group as compared to placebo group from baseline to the end of the trial. There was a trend towards improvement in CSF levels of neurogranin, thought to be a biomarker of synaptic function / dysfunction, in treated patients as compared to placebo group. This, along with the pharmacokinetics and pharmacodynamics study that revealed lower-than-expected numbers of patients who achieved plasma concentrations of drug in the potentially therapeutic dose range, and the trends towards cognitive benefits in patients with higher drug exposure, led to the conclusion of the authors that the dose of neflamapimod was too low for clinical benefits. Another trial with a higher dose (40 mg three times daily) in patients with dementia with Lewy bodies is ongoing (Prins et al., 2021).

AscenD-LB was a randomized blinded trial of neflamapimod in 91 patients with mild to moderate dementia with Lewy bodies (DLB). In the 16-week trial, the patients took either 40 mg of oral neflamapimod twice daily or matching placebo, if under 80 kilograms, or 40 mg of oral neflamapimod three times daily or matching placebo if over 80 kilograms. The primary outcome was change in cognitive function on a neuropsychological test battery. Secondary outcomes included measures of motor function, dementia rating, neuropsychiatric symptoms, and other measures of cognitive function. This was an exploratory trial, and the authors stated that they "reported…p-values for the protocol-specified analyses, though not for the purposes of significance (i.e., hypothesis) testing, rather for the purposes of evaluating the strength of evidence for a treatment effect". They did not adjust p values for multiplicity. Neflamapimod treated patients did not significantly improve on the primary outcome neurological battery, though there were hints towards benefit on the attention subdomain. Those treated with neflamapimod did have a statistically significant improvement on the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) in comparison to placebo from the beginning to the end of the

trial (drug-placebo difference = −0.45, p=0.023). Neflamapimod treatment was associated with improvement in motor function as compared to placebo as measured by time to complete a motor task (drug-placebo difference = −1.4 sec, p=0.044,). There was also a trend towards improvement in hallucinations in neflamapimod treated patients as opposed to placebo treated patients; hallucinations are a hallmark of DLB, making this a potential benefit of interest.

The results of Reverse-SD, which indicated a potentially too-low drug dose, became available while AscenD-LB was ongoing. In line with Reverse-SD, analyses of AscenD-LB suggest potential greater improvement in participants who received higher doses of neflamapimod (three times daily as opposed to two times daily) (Jiang et al., 2022).

DLB is characterized by α-synuclein pathology, known as Lewy bodies, though like AD, DLB can also present with mixed pathology such as α-synuclein and tau pathology. Based on reports that came out while AscenD-LB was ongoing, AscenD-LB investigators also wanted to examine whether neflamapimod was differentially effective in populations with more pure DLB, i.e. only α-synuclein pathology, as opposed to mixed pathology, i.e. α-synuclein and tau pathology. The researchers had baseline plasma samples from 85 of the 91 participants in AscenD-LB. Using a p-tau 181 threshold cutoff of 2.2 pg/mL established by other groups to indicate more pure or mixed pathology, the investigators performed a post-hoc analysis of the response to neflamapimod in patients below and above the plasma p-tau 181 threshold. The researchers found that patients below the p-tau 181 threshold and received higher doses of neflamapimod had greater improvements in assessments of motor function and certain aspects of cognitive function compared to patients receiving placebo. This may indicate that patients with more pure pathology are more responsive to neflamapimod. The authors caution that these analyses are post-hoc, exploratory, and may instead reflect difference in stage of disease during treatment; that is, that patients with lower p-tau 181 levels are also earlier in disease progress, and therefore the disease stage rather than the disease pathology may be mediating the improved response to neflamapimod (Alam et al., 2023). Still, these data may inform future clinical trial design.

A phase 2 trial of MW150 in patients with mild to moderate AD is registered on clinicaltrials.gov; however, this study has not started recruiting. There is no available efficacy data of MW150 in human patients.

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

MW150 and neflamapimod are both inhibitors of p38α kinase. It is hypothesized that p38α may be involved in dementia in a variety of ways. As reviewed by Canovas & Nebreda, 2021, p38α is involved in neuronal excitability, synaptic plasticity, and myelination. Low levels of p38α can be pro-survival and beneficial, but higher levels can lead to inflammation, including the senescence-associated secretory phenotype (SASP), and cell death. Increased phosphorylation of p38α, which reflects levels of active p38α, have been detected in AD brain tissue. p38α is also thought to regulate Aβ plaque formation and deposition and phosphorylate dementia-related proteins such as tau and parkin, the latter of which is a protein associated with Parkinson's disease. Downregulating p38α or p38α activity has resulted in amelioration of neurodegenerative phenotypes in animal models of multiple neurodegenerative diseases, including AD, DLB, PD, and ALS (Gee et al., 2020, reviewed in Canovas & Nebreda, 2021; Jiang et al., 2022; Lin et al., 2022, among others). p38α may play a role in microglial activation, and treatment with preclinical p38 inhibitors has reduced inflammatory markers and microglial activation in cell and animal models (Gee et al., 2020; Lin et al., 2022). Keeping p38α levels in a particular physiological range may therefore have benefits for neurodegenerative diseases.

Another, more recent mechanism of action of neflamapimod in dementia with Lewy bodies (DLB) with potential relevance for other dementias was described by Jiang et al., 2022. Degeneration of the basal forebrain, a brain region involved in cholinergic signaling, is implicated in DLB and other dementias. Cholinesterase inhibitors such as Exelon and Aricept are commonly prescribed in AD and prevent the breakdown of acetylcholine. Addressing the function of cholinergic neurons may offer more clinical benefits than cholinesterase inhibitors. It is hypothesized that one issue affecting the cholinergic system is loss of pro-survival nerve growth factor (NGF) signaling; this signaling is impacted by Rab5, a protein involved in the endosome trafficking system. Hyperactivation of Rab5 causes degeneration of basal forebrain cholinergic neurons (BFCN), impairs NGF signaling and causes BFCN degeneration. p38α is a regulator and activator of Rab5; Jiang and colleagues therefore assessed whether inhibition of p38α could protect against BFCN degeneration via Rab5 in a Down syndrome mouse model that has endosomal pathology and BFCN degeneration. The authors found that treatment with neflamapimod reduced levels of activated Rab5 (Rab5-GTP), mitigated the Rab5 endosomal pathology and loss of BFCN, normalized levels of activated p38α, and resulted in behavioral improvements in mice in measures of memory and anxiety-like behavior. They did not observe any differences in wildtype control animals. It should be noted that due to scarcity of their Down syndrome model animals, they performed and compared behavioral assessments at baseline pre-treatment and then post-4-week treatment. This pre- and post-treatment assessment was performed in both Down syndrome and control mice.

Alam et al., 2015 tested three doses of neflamapimod in aged rats over 17 days. The middle dose, but not the high or low dose, improved cognition, while only the higher dose reduced IL-1β and increased synaptic density in the brain.

Pandey et al., 2022 found that neflamapimod treatment of rats can result in vasodilation; the authors speculated that if this vasorelaxation resulted in systemic blood pressure changes, that it could lead to cognitive benefits. However, no changes in blood pressure have been reported by clinical trials. p38α inhibitors, including neflamapimod, have also been tested in preclinical models of stroke. Neflamapimod treatment post-stroke was found to increase BDNF levels and improve behavioral outcomes in rat model of stroke, and other groups have reported preclinical benefits of p38α inhibitors in stroke. These inhibitors have not yet been explored in clinical stroke contexts (Alam et al., 2020).

In an Alzheimer's mouse model with early synaptic dysfunction in the entorhinal cortex (an area heavily connected to the hippocampus), 14-day treatment with MW150 improved synaptic function and cognition in both young and older animals (Rutigliano et al., 2018). In another Alzheimer's animal model, 14-day treatment with MW150 did not alter plaque load or the expression of immune cell markers (e.g. GFAP and Iba1). However, it did reduce the levels of inflammatory cytokines (IL-1β and TNFα, but not IL-6) and increased the number of microglia surrounding amyloid plaques. *In vitro* studies suggested that MW150 did not affect the migration or phagocytic capacity of microglia (Zhou et al., 2017). Another study reported that MW150 is highly specific for p38αMAPK and does not inhibit CYP enzymes (thus is likely to have few drug interactions). It also improved hippocampal-dependent memory in two Alzheimer's animal models (Roy et al., 2015). Studies of MW150 are reviewed by Roy et al., 2019.

One caveat of these mechanisms is that p38α signaling is complex; while there may be benefits from inhibiting this protein, some groups hypothesize that inhibiting proteins downstream of p38α may have more specific benefits while avoiding unwanted side effects. Some existing inhibitors like neflamapimod are more concentrated in the brain than the plasma (Tormählen et al., 2022), which may mitigate systematic and unwanted side effects; alternate administration routes such as through nasal inhalation may also provide a path towards increased clinical benefit while minimizing adverse events of p38α inhibitors (Casadomé-Perales et al., 2019).

APOE4 interactions:

No clinical studies have examined the interactions, if any, of p38α inhibitors and APOE4 status. Basic science studies have suggested that APOE and p38α signaling pathways interact (Salomon-Zimri et al., 2019), but the clinical significance of this and potential impact of p38α inhibitors is not known.

Aging and related health concerns: Losmapimod may improve certain aspects of atherosclerosis, such as a reduction in plaque inflammation, though a large clinical trial suggests it may not reduce CVD events in a secondary prevention setting.

Types of evidence:

- 1 phase 3 study in patients with an acute myocardial infarction
- 3 phase 2 studies for CVD
- 2 clinical trials for pain
- 1 press release about a clinical trial
- 2 reviews

Cardiovascular disease

Losmapimod was the most advanced p38 MAPK inhibitor in the clinic. It inhibits both the alpha and beta isoforms of p38 MAPK. However, Glaxo-Smith Klein dropped it after disappointing results in clinical trials. Some of the results in different indications follow.

Atherosclerosis

Ninety-nine patients with stable atherosclerosis were treated with placebo or losmapimod (7.5mg/day or bid) for 84 days. Vessel walls with atherosclerotic plaques were measured for vessel inflammation using FDG-PET over consecutive 5mm sections. There was no change in average vessel inflammation. However, when considering only vessel segments with higher levels of inflammation, both doses of losmapimod reduced vascular inflammation. The high dose of losmapimod also reduced serum levels of inflammatory proteins such as IL-8, MCP1, MMP9-NGAL, and the average of hsCRP over time. However, there were no changes in IL-6, MMP9, or hsCRP at the end of the study compared to placebo. hsCRP initially dropped after one week before slowly rising back up. Additionally, the high dose losmapimod reduced visceral but not subcutaneous fat inflammation (Elkhawad et al., 2012). In 57 untreated hypercholesterolemic patients, treatment with losmapimod (7.5mg bid) for 28 days increased

endothelium-dependent and -independent flow-mediated dilation by 25% and 20%, respectively, and increased basal NO synthesis by 10% (Cheriyan et al., 2011).

In a phase 2 study (SOLSTICE), 526 patients who had a non-ST-segment elevation myocardial infarction (NSTEMI) were treated with 7.5mg of losmapimod or placebo bid for 90 days. Treated patients had reduced levels of hsCRP and IL-6 24 hours after treatment, while hsCRP and IL-6 levels between the two groups were equivalent 14 days later. Although there were no differences in death, MI, stroke, or heart failure between the groups, losmapimod-treated patients had improved cardiac function 90 days later as measured by left ventricular ejection fraction, left ventricular end-diastolic, and end-systolic volume (Newby et al., 2014). However, in a larger phase 3 study (LATITUDE-TIMI) in 3,503 patients with an acute myocardial infarction (NSTEMI and STEMI), losmapimod had no effect on primary (Major Adverse Cardiovascular Events) or secondary cardiovascular outcomes. As in the previous study, hsCRP was lower soon after the myocardial infarction in the losmapimod group while the groups were equivalent 90 days later (O'Donoghue et al., 2016). Because of the failure of the phase 3 study, losmapimod was no longer pursued for treatment after an acute myocardial infarction. However, the authors note that since atherosclerosis is associated with inflammation, there is interest in pursuing anti-inflammatory strategies. But the identification of the correct inflammation pathway remains difficult.

Two hypotheses for the failure of the large phase 3 study were put forth by Tun & Frishman, 2018. First, as the study was only 12 weeks in duration, it might have been too short. Additionally, p38B MAPK seems to have beneficial effects (anti-apoptotic, anti-inflammatory). Since losmapimod inhibits both the alpha and beta isoforms of p38 MAPK to a similar extent, a more selective drug may be more beneficial. In summary, losmapimod was beneficial for aspects of atherosclerosis, such as inflammation and flow-mediated dilation, but did not reduce outcomes in large clinical studies.

Pain

Two studies, one in peripheral neuropathic pain the other neuropathic pain due to lumbosacral radiculopahty, reported that losmapimod (7.5mg bid) over 28 days did not alleviate pain symptoms compared to placebo (Ostenfeld et al., 2012; Ostenfeld et al., 2015).

Neflamapimod has been suggested as or explored preclinically for potential cardiovascular indications. For instance, administration of neflamapimod administration in rats was found to result in vasodilation in mesenteric arteries via inhibition of p38α and concomitant downstream signaling; the authors hypothesized that this could potentially lower systemic blood pressure and improve cognitive function

(Pandey et al., 2022). Preclinical work has also suggested that neflamapimod may reduce vascular inflammation (Menon et al., 2023). Whether neflamapimod would have different clinical efficacy when losmapimod was not shown to reduce risk of major cardiovascular events or other cardiovascular outcomes is not known.

p38α inhibitors have also been suggested as a potential combination therapy for cancer, though this is still largely in preclinical stages. Neither neflamapimod nor MW150 have been publicly explored for this purpose (reviewed by Canovas & Nebreda, 2021).

Safety: Studies suggest some risk for elevated liver enzymes for neflamapimod, though larger trials are needed to explore this risk. Common side effects include gastrointestinal disturbances and headache and may include somnolence.

Types of evidence:

- 1 Phase 3 study for losmapimod
- 2 phase 2 studies for neflamapimod
- 1 phase 1 study for neflamapimod
- I review

Overall, the safety profile of neflamapimod is still being established. It appears that headache, diarrhea, and possibly somnolence are some of the most common adverse events associated with neflamapimod treatment. There may be a risk of elevated liver enzymes, and larger trials should clarify this question.

One small open label clinical study in Alzheimer's patients (n=16) reported that 12-week treatment with neflamapimod was safe with mild side effects including diarrhea and somnolence (16% of patients) (Alam et al., 2017). However, EIP Pharma picked up neflamapimod after Vertex dropped the drug due to unacceptable CNS toxicity in animal studies at high doses, though no details were given (press release). Whether it is due to p38α MAPK inhibition, specifically, or off-target effects (neflamapimod also targeted other isoforms of p38 MAPK to a lesser extent) is unknown. In the rheumatoid arthritis trials, a transient increase in liver enzymes was seen in 10-15% of patients, which is apparently a drug class effect (Alam et al., 2015).

Reverse-SD, a randomized controlled trial of neflamapimod in patients with mild AD, enrolled 161 patients. Participants received either 40 mg twice daily of neflamapimod or matching placebo for 24 weeks. The authors did not report statistical analyses of adverse events. The events that occurred in at least 5% of patients, along with their incidence in placebo and treatment group, respectively, were:

- Fall (4% in placebo vs. 6% in neflamapimod;))
- Headache (4% vs. 6%)
- Diarrhea (2% vs. 5%)
- Upper respiratory infection (8% vs. 5%)

The serious adverse events were not thought to be related to the study drug. The serious adverse events in the neflamapimod group were plasma cell myeloma and hyperkalemia. The former event was the one adverse event that led to study drug discontinuation in the neflamapimod group; a fall leading to a subdural hematoma in the placebo group also led to study drug discontinuation. There were no deaths.

One important note is that while the mean changes in alanine and aspartate aminotransferase levels did not show any differences between neflamapimod and placebo groups, one patient on neflamapimod did experience elevations in alanine and aspartate aminotransferase more than three times the upper limit of normal. The enzyme levels had started to resolve within 1 week of the trial; the patient then withdrew from the study. The authors did not report this patient's bilirubin level or whether there were any underlying health conditions or medications that might have been involved in the elevation of the liver enzymes; this information is important for identifying whether this adverse event might be a case relevant for Hy's Law (Prins et al., 2021).

AscenD-LB, published by Jiang et al., 2022, was a randomized, blinded trial of 91 patients with mild to moderate dementia with Lewy bodies (DLB). Participants who were less than 80 kilograms received 40 mg of oral neflamapimod or placebo twice daily; participants who were over 80 kilograms received 40 mg of oral neflamapimod or placebo three times daily. No serious adverse event was considered to be drug related. There were four serious adverse events in the placebo group (hematochezia, internal bleeding, a brain bleed, and asthma exacerbation) and three serious adverse events in the neflamapimod group (a new brain lesion consistent with brain metastasis, new brain tumor diagnosis 34 days after treatment end, and head injury). Three patients in the twice daily neflamapimod group withdrew due to treatment-emergent adverse events (brain lesion and head injury, not considered related; moderate somnolence, considered possibly related), and one patient from the placebo group (hematochezia).

The adverse events that occurred in 5% or more of patients in either placebo- or neflamapimod treated patients, respectively, were:

- falls (9% in placebo, 13% in neflamapimod;)
- headache (4%, 9%,)
- diarrhea (11%, 7%,)
- nausea (7%, 7%)
- tremor (7%, 0%,)

When looking at the patients treated with neflamapimod either two or three times a day, incidence of diarrhea and headache was higher in those receiving three times a day than twice a day.

Adverse Event	Two Times Daily Dosing (Incidence)	Three Times Daily Dosing (Incidence)
Diarrhea	0%	15%
Headache	3%	15%
Falls	19%	5%

A Phase 1 trial of MW150 was reported to be 'safe and well-tolerated' according to a press release by the company, though the press release does not appear to be available any longer (broken link available on AlzForum; also reviewed by Melchiorri et al., 2023).

In a large, 12-week, phase 3 study of losmapimod in patients with acute MI, serious adverse events were similar between the losmapimod and placebo groups (16.0% vs. 14.2%, respectively). The only adverse event differentially reported in the losmapimod group was a non-significant trend toward mildly increased liver enzymes (O'Donoghue et al., 2016).

Drug interactions:

No p38 MAPK drug is approved for clinical use, so drug interactions are not known. Interactions with drugs that may have liver toxicity is something to look for in future trials, given the potential for elevated liver enzymes observed in some patients in some trials of neflamapimod.

Research underway:

There are currently two studies registered on clinicaltrials.gov that are investigating p38α inhibitors. Both studies are enrolling populations with neurodegenerative diseases.

NCT05869669, known as RewinD-LB, is a currently recruiting phase 2b study of neflamapimod in patients with dementia with Lewy bodies (DLB). This randomized, blinded study plans to enroll 160 patients. Participants will take either 40 mg of neflamapimod or placebo by mouth three times daily for 16 weeks. The primary outcome measure is the change in cognitive function as assessed by the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) in patients in the neflamapimod group compared to placebo group. Secondary outcome measures include other measures of cognitive function, motor function, and psychiatric symptoms. One exploratory outcome is brain connectivity as assessed by EEG.

NCT05194163 is a not-yet recruiting study of MW150 in patients with mild to moderate AD. The study aims to enroll 24 patients into the randomized, double-blinded study. Patients will receive oral capsules of either 10 mg of MW150 or placebo daily for 12 weeks. The primary outcome measures of the study focus on safety and tolerability as assessed by laboratory tests, adverse events, ECG, and suicidal ideations. Secondary outcome measures include measures of cognitive function and changes in plasma biomarkers of inflammation and AD. This study is expected to be completed in November 2024.

Search terms:

Pubmed, Google: MW150, neflamapimod, VX-745, losmapimod, p38α inhibitors

- Dementia, AD, dementia with Lewy bodies, cardiovascular, stroke, pain

Websites visited for neflamapimod, MW150, and losmapimod:

- Clinicaltrials.gov: neflamapimod; MW150; losmapimod
- PubChem: neflamapimod; MW150; losmapimod
- DrugBank.ca: neflamapimod; losmapimod
- Cafepharma: neflamapimod; losmapimod

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