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 evidence suggests that p38α MAPK inhibitors may be useful for Alzheimer's and reducing inflammation in cardiovascular disease, but future clinical trials will be needed.

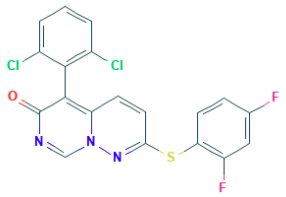
Three main p38α MAPK inhibitors have entered clinical trials. MW150 is a drug funded by ADDF currently in safety studies for Alzheimer's disease. Neflamapimod, developed by EIP Pharma is currently in phase 2 studies for Alzheimer's disease to test efficacy. Losmapimod effectively reduced inflammation in patients with CVD but was abandoned by GlaxoSmithKline after failing to reduce future events.

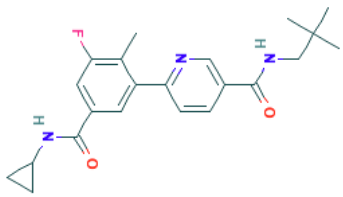
Neuroprotective Benefit: Preclinical studies suggest neuroprotective and anti-inflammatory effects, though no large clinical studies have been conducted.

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 there are no large clinical trials of p38α MAPK inhibitors for Alzheimer's disease.

Availability: Not available in prescription drug form	**Dose**: No currently established dose	**Chemical formula:** $C_{24}H_{23}N_5$ **MW**: 381.47g/mol; **MW150**
Half life: > 3 hours (animals)	**BBB**: penetrant in animals	
Bioavailability: >50% (animals)		
Clinical trials: Phase 1 safety study ongoing	**Observational studies**: None	

Availability: Not available in prescription drug form	**Dose**: 40mg twice per day	**Chemical formula:** $C_{19}H_9Cl_2F_2N_3OS$ **MW**: 436.258g/mol; **Neflamapimod (VX-745)**
Half life: Not reported	**BBB**: penetrant	
Clinical trials: One open-label study completed; two phase 2 efficacy studies underway	**Observational studies**: None	 Source: Pubchem

Availability: Not available in prescription drug form (pharma company halted development)	**Dose**: 7.5mg twice per day	**Chemical formula:** $C_{22}H_{26}FN_3O_2$ **MW**: 383.467g/mol; **Losmapimod (GW8566553X)**
Half life: 7.9-9 hours	**BBB**: Unknown	
Clinical trials: None ongoing	**Observational studies**: None	 Source: Pubchem

What is it? MW150 is a p38α MAPK inhibitor under development by Neurokine Therapeutics. It was invented by ADDF-funded investigator, Dr. Martin Watterson, and ADDF is currently funding 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.

p38α MAPK is a stress-related serine/threonine protein kinase. It is expressed in both neurons and glia, and its phosphorylation may lead to synaptic dysfunction and expression of inflammatory cytokines. Therefore, inhibiting the phosphorylation of p38α MAPK may be both neuroprotective and anti-inflammatory (Alam et al, 2017).

Oxidized LDL is an upstream activator of p38α MAPK which can mediate a vascular inflammatory response in macrophages, and drugs targeting p38α MAPK were developed for cardiovascular disease. Many fatal events associated with atherosclerosis are due to plaque rupture because of thin collagen-poor fibrous caps over an atheroma. Inflammation can contribute to a thin cap formation by inhibiting collagen production from smooth muscle cells as well as promoting collagen degradation (Fisk et al, 2014; Hansson et al, 2015). Losmapimod, a p38α and p38β MAPK inhibitor, failed in a cardiovascular clinical trial and was subsequently dropped.

Many first-generation p38α MAPK inhibitors were associated with off-target side effects due to the difficulty in selective targeting of kinases (Libby and Everett, 2019). Neurokine and Vertex developed MW150 and neflamapimod as more selective drugs with the hope of mitigating some of these effects.

Neuroprotective Benefit: Preclinical studies suggest neuroprotective and anti-inflammatory effects, though no large clinical studies have been conducted.

Types of evidence:

- *Multiple pathology studies in Alzheimer's brain tissue*
- *One open-label clinical study of neflamapimod in Alzheimer's patients*
- *Three preclinical studies of MW150*

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

Phosphorylated-p38 (p-p38) MAPK expression was increased in the patients with early Alzheimer's disease (Braak stages IV-V), and in some later Alzheimer's disease 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 increased transiently. There was no correlation between p-p38 MAPK and amyloid plaques (Sun et al, 2003). However, an earlier 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 p-MKK6, an upstream activator of p38 MAPK, was 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:

Neflamapimod – In an open-label clinical study over 84 days with two doses of neflamapimod (40 or 125mg twice per day), 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 40mg group and 1 responder (out of 7 patients) in the 125mg 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.

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

MW150 - 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 a, 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 p38α MAPK and does not inhibit CYP

enzymes (thus may have few drug interactions). It also improved hippocampal-dependent memory in two Alzheimer's animal models (Roy et al, 2015).

Neflamapimod – Preclinical results of neflamapimod are unclear. 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.

APOE4

No information

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 cardiovascular (CVD) events in a secondary prevention setting.

Types of evidence:

- *One phase 3 study in patients with an acute myocardial infarction*
- *Three phase 2 studies for CVD*
- *Two clinical trials for pain*

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, GlaxoSmithKline 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 twice per day) 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 twice per day) 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 twice per day 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.

Two hypotheses for the failure of the large phase 3 study were put forth by Tun and Frishman (2018). First, as the study was only 12 weeks in duration, it might have been too short. Additionally, p38β 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 twice per day) over 28 days did not alleviate pain symptoms compared to placebo (Ostenfeld et al, 2012; Ostenfeld et al, 2015).

Safety: Studies suggest some risk for elevated liver enzymes, though there are no large clinical trials of p38α MAPK inhibitors for Alzheimer's disease.

Types of evidence:

- One phase 3 study for losmapimod
- One phase 1 study for neflamapimod

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 may bea drug class effect (Alam et al, 2015).

MW150 is currently undergoing a safety study.

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. Given the trends toward increased liver enzymes, any drug that may damage the liver should probably not be used at the same time.

Sources and dosing:
Neflamapimod is in clinical development at 40mg twice per day with food. MW150 is currently in dose-finding studies.

Research underway:
MW150 is currently in a clinical study testing safety. This study is being funded by ADDF.

There are two neflamapimod clinical trials ongoing. NCT03402659 is a phase 2b efficacy study testing 40mg bid in 150 Alzheimer's patients. NCT03435861 is a phase 2a study testing the effect of 40mg in 40 patients to look at changes in brain inflammation (TSPO PET).

Search terms:

Pubmed:

- MW150
- neflamapimod
- vx-745
- losmapimod

Given that there are few published studies for these drugs, and unrestricted search was conducted.

Websites visited for

- Clinicaltrials.gov
- Drugs.com
- DrugBank.ca
- Pubchem