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.

Crisdesalazine

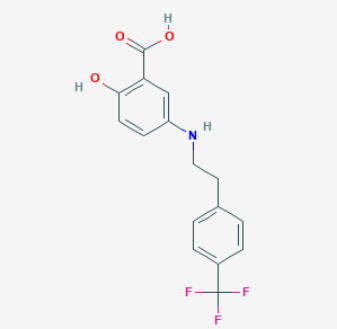
Evidence Summary

Crisdesalazine improved cognition in old dogs and showed neuroprotective benefit in mouse models of AD and ALS. Only a phase 1 trial has been carried out in humans, so long-term safety is unknown.

Neuroprotective Benefit: mPGES-1 is increased in the brains of Alzheimer's patients. Crisdesalazine improved cognitive functions in old dogs, inhibited neuronal loss and lipid peroxidation in a mouse model of AD, and was neuroprotective in ALS mice.

Aging and related health concerns: Crisdesalazine increased survival in a mouse model of ALS. Preclinical studies suggest mPGES-1 inhibition may benefit cancer, arthritis, atherosclerosis, and neuropathy, but may also cause harm in some cell types.

Safety: Only a phase I study has been completed, so long-term safety in humans is unknown. In older dogs, crisdesalazine treatment did not result in adverse events related to the drug. In mice, a 1,000 mg/kg dose did not cause gastric bleeding.

Availability: not available, under clinical development	**Dose**: Based on a phase I study, the expected therapeutic dose for Alzheimer's disease is 50 mg per day.	**Chemical formula:** $C_{16}H_{14}F_3NO_3$ **MW**: 325.25  Source: PubChem
Half life: not documented	**BBB**: not documented	
Clinical trials: Only a phase I single ascending dose trial has been completed to date.	**Observational studies**: N/A	

What is it? Crisdesalazine (also known as AAD-2004) is an inhibitor of microsomal prostaglandin E2 synthase-1 (mPGES-1) that also has reactive oxygen species scavenging actions (GNT Pharma website). It is under development by GNT Pharma Co., Ltd (South Korea) for Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), major depression, and canine dementia. Prostaglandin E2 (PGE2) is the most common prostaglandin in the brain and contributes to physiological and pathophysiological brain functions (Ikeda-Matsuo 2017). Under physiological conditions, PGE2 modulates neuronal excitation, plasticity, neuronal proliferation and differentiation, dendritic spine formation, and learning and memory. Under pathological conditions, excess PGE2 is produced in lesion sites in the brain.

PGE2 is derived from membrane phospholipids, which are converted to arachidonic acid by cPLA2, then conversion to PGH2 by COX-1/COX-2. COX-2 produces not only PGE2, but other prostanoids including PGI2, PGD2, PGF2α and thromboxane A2. Of the 3 isoforms of PGES (cytosolic PGES, mPGES-1, and mPGES-2), only mPGES-1 is an inducible enzyme for PGE2 synthesis, converting PGH2 to PGE2. After synthesis, PGE2 can activate 4 G-protein-coupled receptors, EP1–EP4; EP1 and EP3 receptors appear to be essential for the neurotoxicity mediated by PGE2, while the EP2 receptor activation appears to be protective (Ikeda-Matsuo 2017).

Compared to COX-1/COX-2 inhibition, mPGES-1 inhibition specifically inhibits the production of PGE2 and not other prostanoids, and therefore is expected to have fewer gastrointestinal, renal and

cardiovascular side-effects. mPGES-1 is induced in the delayed phase of inflammation, and is involved in wakefulness, inflammation, hyperalgesia, pain, fever, and cancer (Chaudhry et al., 2008). mPGES-1 expression, together with that of COX-2, is induced by proinflammatory stimuli such as IL-1β and can be downregulated by anti-inflammatory glucocorticoids, docosahexaenoic acid, and eicosapentaenoic acid.

Part of the challenge of developing selective inhibitors for mPGES-1 has stemmed from the fact that seemingly potent inhibitors towards recombinant human mPGES-1 can display a significant loss in potency in human blood and low bioavailability *in vivo* (Bergqvist F et al., 2020). This is likely due to high non-specific plasma protein binding. The other hurdle has been that inhibitors designed for human mPGES-1 typically lacks or have significantly decreased potency towards mouse and rat mPGES-1.

Neuroprotective Benefit: mPGES-1 is increased in the brains of Alzheimer's patients. Crisdesalazine improved cognitive functions in old dogs, inhibited neuronal loss and lipid peroxidation in a mouse model of AD, and was neuroprotective in ALS mice.

Types of evidence:

- 2 postmortem human studies examining mPGES-1 expression
- 3 animal studies testing crisdesalazine (1 in dogs, 2 in mice)
- Numerous laboratory studies examining the role of mPGES1

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

No studies have tested crisdesalazine for prevention of dementia or cognitive decline in humans.

Two postmortem studies have compared mPGES-1 expression in the brains of Alzheimer's patients vs healthy controls. In one study, postmortem middle frontal gyrus tissue was collected from10 sporadic Alzheimer's disease, 10 familial Alzheimer's disease, and 9 age-matched control individuals (Chaudhry et al., 2008). mPGES-1 expression analyzed by Western blot was significantly elevated in tissue from Alzheimer's patients, on average by 3-fold. In brains from age-matched control cases, mPGES-1 was constitutively expressed in microglia, astrocytes, neurons, and endothelium but not in smooth muscle cells. mPGES-1 expression appeared to vary in sporadic Alzheimer's cases, whereas familial Alzheimer's cases appeared to have a more consistent level of intensity. In end-stage Alzheimer's disease, mPGES-1 appeared to be markedly elevated in pyramidal neurons while diminished or absent in astrocytes. In both control and Alzheimer's brains, mPGES-1 expression colocalized with Aβ42.

In the other human postmortem study, mPGES-1 was also induced and colocalized with Aβ plaques in the cerebral cortex (Akitake et al., 2013).

Human research to suggest benefits to patients with dementia:
No studies have tested crisdesalazine in patients with dementia.

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

Crisdesalazine in AD models: A press release by GNT Pharma on a study of 48 companion dogs with severe cognitive dysfunction reported that crisdesalazine treatment (5 or 10 mg/kg) for 8 weeks significantly improved the canine cognitive dysfunction rating scale (primary outcome) and canine dementia scale (secondary outcome) compared to the placebo group (BusinessWire.com).

In a mouse model of Alzheimer's (Tg-βCTF99/B6 mice), crisdesalazine treatment (25 mg/kg/day, in food) for 8 months starting from 10 months of age inhibited the accumulation of lipid peroxidation and suppressed neuronal loss and neuritic atrophy (Baek et al., 2013). This mouse model displays age-dependent neuronal loss and neuritic atrophy in the brain; at 10 months of age, there is no obvious neuronal loss, but by 18 months of age, there is some loss of neurons. The cell density in the prefrontal cortex and the parietal cortex of the brains of Tg-βCTF99/B6 mice was reduced to, respectively, 87% and 89% of the non-transgenic control mice, whereas in the crisdesalazine-treated mice, the cell density was at 94% and 96%, respectively, of control mice. mAPP, calbindin, phospho-CREB, and transthyretin levels were also compared between treated versus control in transgenic and non-transgenics, but these differences were not analyzed statistically.

Crisdesalazine in ALS models: In a mouse model of ALS (SOD1G93A transgenic mice), crisdesalazine treatment (2.5 mg/kg, orally twice daily) started at 8 weeks of age blocked free radical production (levels of nitrotyrosine and 8-OHdG), PGE2 formation, and microglial activation (Iba-1 expression) in the spinal cords (Shin et al., 2012). Crisdesalazine also reduced autophagosome formation (conversion of LC3-I to LC3-II), axonopathy, and motor neuron degeneration, while improving motor function and increasing life span. Crisdesalazine also blocked the abnormal aggregation of mutant SOD1 observed in the lumbar spinal cord of SOD1G93A mice. Crisdesalazine treatment was superior to riluzole (50 mg/kg) or ibuprofen (25 mg/kg, twice daily) on motor function, onset of rotarod deficit, and survival. The onset of rotarod deficit was delayed by 12%, 15.6%, and 36% in the riluzole-, ibuprofen-, and crisdesalazine-treated groups, respectively, as compared with the vehicle group. Survival was extended by 8.2%, 9.4%, and 21% in the riluzole-, ibuprofen-, and crisdesalazine-treated groups, respectively.

In vitro, crisdesalazine blocked free radical neurotoxicity as a potent spin-trapping molecule (Shin et al., 2012). Cortical cultures containing neurons and glia exposed to 50 µM Fe2+ produced reactive oxygen species within 4 hours and neuronal death over 24 hours. Concurrent addition of 1 µM crisdesalazine blocked Fe2+-induced reactive oxygen species production and neuronal death with greater efficacy and potency compared to other antioxidants examined (vitamin E, estrogen, melatonin, and acetyl-L-carnitine). Thus, concurrent blockage of free radicals and PGE2 may be beneficial for treating ALS.

Studies evaluating the role of mPGES-1: In experimental animal models and patients with brain diseases, mPGES-1 is upregulated in the sites of lesion (Ikeda-Matsuo 2017). Basal mPGES-1 expression in the brain appears to be very low.

In a mouse model of Alzheimer's disease (Tg2576 mice), mPGES-1 deletion reduced the accumulation of microglia around senile plaques and attenuated learning impairments (Akitake et al., 2013).

In postmortem Parkinson's patients and in animal models of Parkinson's, PGE2 accumulates in the substantia nigra. In a rat model of Parkinson's (intranigral LPS injection), mPGES-1 was induced in activated ameboid microglia in the substantia nigra (Ikeda-Matsuo et al., 2005).

In rodent models of ischemic stroke (e.g., middle cerebral artery occlusion-reperfusion model), mPGES-1 and COX-2 are induced and colocalized in the core and peri-infarct regions. In mPGES-1 deficient mice, ischemic injuries such as infarction, edema, and apoptotic cells were significantly reduced compared to those in wild-type mice (Ikeda-Matsuo et al., 2006). Deletion of mPGES-1 also ameliorated behavioral symptoms observed after ischemia, such as neurological dysfunction and reduction in locomotor activity.

APOE4 interactions: Unknown.

Aging and related health concerns: Crisdesalazine increased survival in a mouse model of ALS. Preclinical studies suggest mPGES-1 inhibition may benefit cancer, arthritis, atherosclerosis, and neuropathy, but may also cause harm in some cell types.

Types of evidence:

- No studies testing crisdesalazine in humans
- 1 study in a mouse model of ALS examining survival
- Numerous laboratory studies on the role of mPGES-1

Lifespan: INCREASED IN A MOUSE MODEL OF ALS
In a mouse model of ALS (SOD1G93A transgenic mice), crisdesalazine treatment (2.5 mg/kg, orally twice daily) started at 8 weeks of age improved axonopathy and increased lifespan (Shin et al., 2012). Crisdesalazine treatment was superior to riluzole (50 mg/kg) and ibuprofen (25 mg/kg, twice daily) on survival; survival was extended by 8.2%, 9.4%, and 21% in the riluzole-, ibuprofen-, and crisdesalazine-treated groups, respectively.

Studies from other mPGES-1 inhibitors: POTENTIAL BENEFIT IN PRECLINICAL MODELS OF CANCER
In a mouse model of skin cancer (xenografts of skin cancer A431 cells), treatment with human mPGES-1 inhibitor AF3485 decreased epidermal growth factor receptor (EGFR) signaling and vascular endothelial growth factor (VEGF) expression *in vitro* and *in vivo*, which limited tumor growth (Finetti et al., 2012). In models of neuroblastoma, daily treatment with CIII, an mPGES-1 inhibitor with cross-species activity, reduced tumor growth, which correlated with reduced angiogenesis and less infiltration of cancer-associated fibroblasts (Kock et al., 2018). However, neither NSAIDs nor mPGES-1 inhibitors alone resulted in complete inhibition of tumor growth. Inhibitors of mPGES-1 are therefore not anticipated as single treatment in cancer. mPGES-1 inhibitors are thought to have anti-carcinogenic effects via several mechanisms including decreased cancer cell proliferation, decreased tumor angiogenesis, promotion of anti-cancer macrophage polarization, re-activation of cytotoxic T cells, and synergism with conventional therapy (Bergqvist F et al., 2020).

Studies on the role of mPGES-1: mPGES-1 KNOCKOUT CAN BE BENEFICIAL OR HARMFUL, DEPENDING ON MODEL AND CELL TYPE
Studies from mPGES-1 deficient mice provide evidence for its role in a variety of inflammatory and cardiovascular diseases, though the evidence can be mixed depending on the model used, or the cell type targeted.

For example, mice lacking mPGES-1 have decreased incidence and disease severity in one model of arthritis (collagen-induced), but in another model (collagen antibody-induced), increased disease incidence and higher disease score was observed (Bergqvist F et al., 2020). Also, in an osteoarthritis model, no difference was observed in cartilage destruction score in mPGES-1 knockout mice.

mPGES-1 deficient mice have reduced mechanical allodynia and thermal hyperalgesia following nerve damage in a model of neuropathic pain (Bergqvist F et al., 2020).

In models of atherosclerosis, mPGES-1 deletion specifically in myeloid cells retarded disease progression, while deletion in endothelial cells or vascular smooth muscle cells showed neutral effects (Wang et al., 2006; Chen et al., 2014). Studies in a model of vascular injury also showed retarded disease progression with mPGES1 deletion in myeloid cells, but deletion of mPGES-1 in vascular smooth muscle cells or endothelial cells caused worse responses (intimal thickening, vascular stenosis, and leukocyte infiltration)(Chen et al., 2013).

Other models where deletion of mPGES-1 was shown to be harmful include a model of colon injury (DSS-induced) where more severe disease was observed and T-cell dependent induced colitis model.

Cancer: mPGES-1 INCREASED IN CANCER
Crisdesalazine has not been tested in any cancer.

Elevated levels of mPGES-1, COX-2, and PGE2 have been observed in several different cancers, including colon cancer, non-small cell lung cancer, and prostate cancer, and have been shown to mediate the proliferation, survival, invasiveness, and angiogenic potential of tumor cells (Ikeda-Matsuo 2017).

In human glioma, overexpression of mPGES-1 (as well as mPGES-2 and cPGES) was observed in both low- and high-grade tumors (Mattila et al., 2009). There were no correlations between tumor grade and PGES staining of tumor cells or vascular endothelium, except in oligodendrogliomas where a moderate correlation was found between tumor grade and tumor cell staining with mPGES-1 and cPGES.

Another study reported that high-risk neuroblastoma, in particular the therapy-resistant subset with chromosome 11q-deletion, was characterized by high expression of the COX/mPGES-1/PGE2 pathway that correlates with metastatic stage and poor clinical outcome (Larsson et al., 2015). Also, infiltrating cancer-associated fibroblasts expresses mPGES-1, which may contribute to tumor growth, angiogenesis, and metastatic spread.

Safety: Only a phase I study has been completed, so long-term safety in humans is unknown. In older dogs, crisdesalazine treatment did not result in adverse events related to the drug. In mice, a 1,000 mg/kg dose did not cause gastric bleeding.

Types of evidence:

- 1 phase I trial
- 1 review of mPGES-1 inhibitors
- 3 animal studies (1 in dogs, 2 in mice)

Clinical phase 1 single ascending dose trial in humans has been completed (GNT Pharma website). Safety was verified in 4 cohorts (20, 50, 100, and 200 mg), though no details on the results have been released.

A press release by GNT Pharma on a study of 48 companion dogs with severe cognitive dysfunction reported that crisdesalazine treatment (5 or 10 mg/kg) for 8 weeks did not result in adverse events related to the drug (BusinessWire.com).

In a mouse model of ALS (SOD1G93A transgenic mice), oral administration of crisdesalazine at a dose of 1,000 mg/kg, 400 times higher than the maximal therapeutic dose, did not damage gastric mucosal membrane (Shin et al., 2012).

In a review of mPGES-1 inhibitors, some concerns for safety were raised (Bergqvist F et al., 2020). Drug development for mPGES-1 inhibitors has been slow due to the lack of potent inhibitors with cross-species activity, and only a few mPGES-1 inhibitors have been tested in humans. The results from the first phase I trial of an mPGES-1 inhibitor, the Eli Lilly compound LY3023703, showed that while it dose-dependently inhibited PGE2 production in human whole blood *ex vivo*, 1 subject developed drug-induced liver injury as measured by elevated levels of serum alanine aminotransferase levels upon taking 30 mg/day of LY3023703 for 28 days. A follow-up compound, LY3031207, was tested in a phase I trial but the study was terminated when several subjects developed drug-induced liver injury. The investigators concluded in a follow-up study that the toxicity was unlikely due to the mPGES-1/PGE2 target, but instead, caused by conversion of the inhibitors into toxic metabolite(s).

However, in the same review, the authors note that the widely used NSAIDs, which inhibit COX activity resulting in decreased PGE2 production and symptomatic relief, block the production of many other lipid mediators that have important physiological and resolving actions (Bergqvist F et al., 2020). NSAIDs can cause gastrointestinal bleeding and/or increase the risk for severe cardiovascular events. Selective

inhibition of downstream mPGES-1 that would selectively reduce PGE2 production is suggested as a safer therapeutic strategy.

Drug interactions: Drug interactions have not been studied or documented.

Sources and dosing: Crisdesalazine is under clinical development by GNT Pharma in South Korea for Alzheimer's disease, Parkinson's disease, ALS, and/or depression. Based on the phase I single ascending dose study testing 20, 50, 100, and 200 mg doses of crisdesalazine, the expected therapeutic dose for Alzheimer's disease was predicted to be 50 mg.

Research underway: GNT Pharma is developing crisdesalazine for Alzheimer's disease, Parkinson's disease, ALS, and/or depression, as well as for canine dementia. Clinical phase 1 single ascending dose trial in humans has been completed (GNT Pharma website).

Search terms:
Pubmed, Google: crisdesalazine, AAD-2004, mPGES-1

Websites visited for crisdesalazine, AAD-2004:

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

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