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.

Dapansutrile (OLT1177)

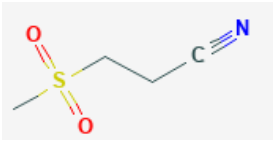
Evidence Summary

NLRP3 inflammasome inhibitor with oral bioavailability and good short-term safety. It reduces IL-1β mediated peripheral inflammation and may benefit osteoarthritis, but more long-term safety data are needed.

Neuroprotective Benefit: May decrease IL-1β mediated inflammatory damage due to peripheral immune cell infiltration into the CNS. Unclear whether it can inhibit microglial activation directly.

Aging and related health concerns: Based on short clinical studies, it may reduce acute arthritis-associated joint pain and inflammation, and is potentially protective in the context of heart failure based on a preclinical study.

Safety: Not associated with adverse events in acute studies, but long-term studies with chronic dosing have not been conducted. Possible increased risk for infection.

Availability: In clinical trials	**Dose**: Not established	**Chemical formula:** $C_4H_7NO_2S$ **MW**: 133.17 g/mol  Source: PubChem
Half-life: ~24 hours (in plasma)	**BBB**: Likely Penetrant. Not documented, but has properties associated with penetrance	
Clinical trials: Phase 1 in healthy adults (n=36, n=35); Phase 2 in arthritis (n=202, n=79, n=29).	**Observational studies**: None	

What is it?

Dapansutrile is an **inhibitor of the NLRP3 inflammasome** being developed for inflammatory conditions as OLT1177™ by Olatec Therapeutics. The NLRP3 inflammasome is activated in response to various danger signals, such as pathogen-associated molecular patterns (PAMPs) released by microbial agents and damage-associated molecular patterns (DAMPs) released by stressed cells [1]. The activated NLRP3 inflammasome then promotes caspase-1 dependent production of the inflammatory cytokines IL-1β and IL-18, as well as a form of programmed cell death called pyroptosis. The activation of the NLRP3 inflammasome is a two-step process involving a priming signal that leads to the upregulation of NLRP3 and pro-IL1β, and a second signal which induces oligomerization and activation. Dapansutrile acts by inhibiting the second part, thereby preventing NLRP3 inflammasome oligomerization and the release of mature IL-1β, without affecting *nlrp3* or *il1b* gene expression [2]. Dapansutrile can also reduce levels of the pro-inflammatory cytokine IL-6 since IL-1β is a known inducer of IL-6 [3], but typically does not affect levels of TNFα. Dapansutrile does not affect the activity of related inflammasomes NLRC4 or AIM2 [2], and is thought to be specific for NLRP3, though more work is needed to confirm the specificity *in vivo*. Dapansutrile satisfies Lipinski's rule of five (IUPHAR/BPS), and has been shown to have good oral bioavailability in humans [2]. It has been tested in clinical trials in a topical gel formulation for osteoarthritis, and as an oral capsule formulation for gouty arthritis.

Neuroprotective Benefit: May decrease IL-1β mediated inflammatory damage due to peripheral immune cell infiltration into the CNS. Unclear whether it can inhibit microglial activation directly.

Types of evidence:

- 1 laboratory study

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function? None

Human research to suggest benefits to patients with dementia: None

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

The NLRP3 inflammasome is abundantly expressed by microglia and astrocytes, and plays a role in innate immune responses in the CNS [4]. The **NLRP3 inflammasome is activated in response to oxidative stressors, and chronic activation may play a role in the programming of microglia** toward a hyperactive state associated with increased release of pro-inflammatory cytokines [5]. Mitochondria-related pathology can induce a shift from oxidative phosphorylation, which promotes tolerogenic (non-reactive) microglia toward aerobic glycolysis, which is associated with oxidative stress and promotes pathogenic microglia. NLRP3 inhibition, then, can reduce the inflammatory response associated with chronic mitochondrial stress. A study examining the effect of systemic administration of dapansutrile in mice found that treatment increased flux through the pentose phosphate pathway and promoted mitochondrial metabolism in muscle tissue [2]. This suggests that dapansutrile may potentially also help correct the metabolic impairment that is driving the induction of pro-inflammatory reactive glia.

Activation of the NLRP3 inflammasome is implicated in driving IL-1β mediated inflammation and pyroptotic cell death in a variety of neurodegenerative diseases, and NLRP3 inhibition has been shown to be protective in various preclinical models [4] (see NLRP3 Inhibition report). Although the Olatec website indicates that dapansutrile has been tested in neurodegenerative and CNS disease models, the only published evidence for its role in the CNS is in a mouse model of multiple sclerosis. In this study, dapansutrile induced NLRP3 inhibition was evident in the spinal cord [6], suggesting that it can cross the blood-spinal cord barrier. The molecular weight, polar surface area, and number of hydrogen bond acceptors found in dapansutrile also suggest it is likely CNS penetrant, but **experiments directly measuring dapansutrile levels in the CSF and/or CNS tissue have not been published**. Additionally, multiple sclerosis is associated with blood-CNS barrier leakiness [7], and the reduction in NLRP3 activation could be due to the decreased infiltration of peripheral immune cells into the CNS, rather

than a direct effect on CNS resident cells, as IL-1β is known to play a role in BBB permeability [8]. Therefore, at this time, it is not clear whether dapansutrile is the optimal NLRP3 inhibitor for neurodegenerative diseases.

Multiple sclerosis: Potential benefit (preclinical)

Dapansutrile was tested in a mouse model of chronic experimental autoimmune encephalomyelitis (EAE) induced by active immunization with a MOG peptide, a myelin-associated protein [6]. When administered prophylactically in the diet (3.5 g/kg food) starting at the time of immunization, dapansutrile reduced the infiltration of CD4+ T cells and macrophages into the spinal cord, as well as spinal cord levels of the pro-inflammatory cytokines IL-1β, IL-18, and IL-6. This was accompanied by a 2-fold reduction in spinal cord demyelination, and a reduction in neurological deficits. When administered as a treatment starting at the onset of neurological symptoms, dapansutrile was also protective, but only with twice daily administration (60 mg/kg i.p. or oral gavage). This study suggests that NLRP3 inhibition with dapansutrile may be beneficial at reducing CNS pro-inflammatory cytokines derived from peripheral sources.

APOE4 interactions: Not known

Aging and related health concerns: Based on short clinical studies, it may reduce acute arthritis-associated joint pain and inflammation, and is potentially protective in the context of heart failure based on a preclinical study.

Types of evidence:

- 3 clinical trials (2 Phase 2 RCTs for knee osteoarthritis n=79, n=202; 1 Phase 2 PoC in gouty arthritis n=29).
- 2 laboratory studies

Osteoarthritis: Potential benefit

Osteoarthritis is associated with joint pain following the degeneration of protective cartilage (Mayo Clinic). It is a non-autoimmune form of arthritis, and the risk for developing osteoarthritis increases with age.

A topical gel formulation of dapansutrile has been tested in two placebo-controlled Phase 2 RCTs in patients with knee osteoarthritis. The results of these trials have not been posted, but according to the Olatec website, patients treated with dapansutrile in both the 2-week dose finding study (n=79, gel administered TID) (NCT01768975) and the 6-week study (n=202, 6 mL of 5% gel administered TID) (NCT02104050) exhibited a reduction in knee pain at a level considered to be clinically meaningful based on the literature [9]. However, these trials were completed in 2013 and 2015, respectively, and it is unclear why the full results have not been made publicly available.

Gouty arthritis: Potential benefit

Gout is a form of arthritis that develops due to the buildup of uric acid crystals in the joints (Mayo Clinic). It is typically associated with the release of pro-inflammatory cytokines by cells of the synovial lining and an associated infiltration of neutrophils into the joint cavity [10]. The NLRP3 inflammasome has been found to be involved in gout-associated inflammation, and IL-1 inhibitors are currently approved for the treatment of gout.

An oral formulation of dapansutrile has been tested in a Phase 2a proof-of-concept study in patients with acute gout flares (n=29) (EudraCT Number: 2016-000943-14). Results based on the dosing of the first three cohorts (500 mg BID, 500 mg QID, 300 mg divided into 200mg at 8hr and 100 mg at 20hr) were presented at the EULAR rheumatology conference in 2019 [11]. **A clinical response, measured by disability scores and the Visual Analog Scale for pain, was reported in patients at all dosing regimens**. An associated mechanistic study found that markers of inflammation, C-reactive protein and serum amyloid A, were dose dependently decreased over the 7-day treatment course [12]. Peripheral blood mononuclear cells (PBMCs) isolated from patients and stimulated *ex vivo* showed **decreased production of mature IL-1β, indicative of NLRP3 inhibition *in vivo***.

Dapansutrile (600 mg/kg) also reduced joint inflammation in a mouse model of gouty arthritis (monosodium urate injection), when administered prophylactically or 1 hour following the urate injection [10]. Treatment reduced inflammatory immune cell infiltration and synovial levels of pro-inflammatory cytokines and chemokines (IL-1β, IL-6, MPO, CXCL1). Notably, the plasma levels of dapansutrile associated with efficacy in the mice were within range of the plasma levels in humans after oral intake of doses found to be safe in a Phase 1 study.

Heart injury: Potential benefit (preclinical)

NLRP3 inflammasome activation in the context of a heart ischemic-reperfusion injury can activate caspase-1 mediated pyroptotic cell death and promote the loss of myocardial tissue [13]. While

dapansutrile had no effect on heart contraction, based on left ventricular ejection fraction, in wild-type mice, it preserved left ventricle systolic function in mice examined 24 hours after myocardial ischemic-reperfusion injury [14]. Dapansutrile (600 mg/kg i.p.) was protective when administered at the time of reperfusion following both a short (30 minute) and long (75 minute) bout of ischemia, and when administered up to 1 hour after reperfusion. This suggests that dapansutrile **may have a therapeutic window conducive to use in a clinical setting.** The protective effect on heart function was associated with a ~50% reduction in caspase-1 activation and reduction in infarct size.

A Phase 1b placebo-controlled trial for the use of oral dapansutrile capsules in heart failure patients is currently ongoing (NCT03534297).

Safety: Not associated with adverse events in acute studies, but long-term studies with chronic dosing have not been conducted. Possible increased risk for infection.

Types of evidence:

- 5 clinical trials (3 RCT for topical gel formulation one Phase 1 in healthy adults, n=36 + two Phase 2 in osteoarthritis (n=79, n=202); Two trials for oral formulation one Phase 1 in healthy adults n=35, one Phase 2 in gouty arthritis n=29)
- Several laboratory studies

Dapansutrile has been tested in five clinical trials (3 for a topical formulation, and 2 for an oral capsule formulation), and according to the information disclosed by Olatec Therapeutics, was found to exert a good safety profile, although the full safety results have only been published for the Phase 1 study of the oral capsules in healthy adults (n=35) [2]. No treatment-emergent serious adverse events have been reported. All of the adverse events were determined to be unrelated to the drug and resolved spontaneously. There were **no significant changes in hematological parameters, serum lipids, urinalysis, liver function enzymes, or physical examination measures with doses up to 1000 mg for 8 days**. In patients with acute gout flares, there were no reported metabolic, physiological, or hematological changes, and all tested doses (up to 2000 mg/day for 8 days) were well-tolerated [11].

The primary safety concern, which would not be captured by these short-term studies, is the risk for infection. The NLRP3 inflammasome is activated in response to numerous bacterial, fungal, and viral pathogens, and plays an important role in the inflammatory immune response toward these pathogens [1]. Consequently, chronic NLRP3 inhibition could lead to a dampened immune response toward this

subset of pathogens, leading to an increased risk for chronic infections, or complications stemming from the inability to adequately clear these pathogens. While short-term administration during acute flares of inflammation appears to be safe [11], it is not known at this time whether long-term administration of oral (systemic) dapansutrile would lead to immune suppression, or additional adverse events.

Since NLRP3 is important for the production of IL-1β it would be expected to have a similar drug-interaction profile with anti-IL-1 therapies, which has major interactions primarily with other therapeutic agents that target the immune system and could lead to immune suppression (Drugs.com).

Sources and dosing:

Dapansutrile is being developed as OLT1177™ by Olatec Therapeutics. It has not yet been approved for any indication, and continues to undergo clinical testing to determine doses that are both safe and clinically effective. Orally administered dapansutrile was found to be safe for acute administration up to 8 days in healthy adults at doses up to 1000 mg per day. This dose led to drug plasma levels that were within the range of those associated with benefit in preclinical models. Due to the relatively long half-life (~24 hours), there is accumulation of the drug with consecutive daily dosing [2].

Research underway:

According to Clinicaltrials.gov, there are currently two active clinical trials for dapansutrile.

Dapansutrile is being tested in a placebo-controlled Phase 1 RCT in patients with heart failure, which has an estimated completion date in February 2020 (NCT03534297).

Dapansutrile is being tested in a pilot, open-label Phase 2 trial in patients with Schnitzler Syndrome, which is a rare autoinflammatory disorder involving joint pain typically treated with anti-IL-1 therapies. The trial has an estimated completion date in August 2020 (NCT03595371).

Search terms:

Pubmed, Google: Dapansutrile, OLT1177 +

- NLRP3, neurodegeneration, aging, arthritis, inflammation, cardiovascular, safety, clinical trials

Websites visited for Dapansutrile (OLT1177):

- Clinicaltrials.gov
- PubChem

- IUPHAR/BPS Guide to Pharmacology

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