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)

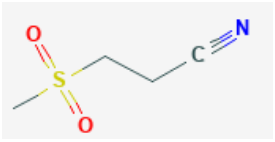
Evidence Summary

This NLRP3 inflammasome inhibitor has oral bioavailability and good short-term safety, but no long-term data. It reduces IL-1β mediated peripheral inflammation, and is best suited to earliest disease stages.

Neuroprotective Benefit: It may decrease IL-1β mediated inflammatory damage by preventing the metabolic reprogramming of immune cells toward a pro-inflammatory state and infiltration of peripheral immune cells into the CNS.

Aging and related health concerns: Based on short clinical studies, it may reduce acute arthritis or gout-associated pain and inflammation. Benefits are most apparent when given prophylactically or at injury onset to prevent inflammatory damage.

Safety: Not associated with adverse events in acute studies, but long-term studies with chronic dosing have not been conducted. There is a 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**: Penetrant	
Clinical trials: Phase 1 trials in healthy adults (n=36, n=35), a Phase 1b trial in heart failure (n=30), and Phase 2 trials in osteoarthritis (n=202, n=79, n=29) have been completed.	**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-IL1 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, and for heart failure. Olatec holds patents for using dapansutrile as a treatment for inflammatory skin conditions, inflammation and pain, and multiple sclerosis.

Neuroprotective Benefit: It may decrease IL-1β mediated inflammatory damage by preventing the metabolic reprogramming of immune cells toward a pro-inflammatory state and infiltration of peripheral immune cells into the CNS.

Types of evidence:

- 3 laboratory studies

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:
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). 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. However, is not clear whether dapansutrile is the optimal NLRP3 inhibitor for neurodegenerative diseases.

Alzheimer's disease: POTENTIAL BENEFIT AT EARLY STAGES (Preclinical)
Brain and serum levels of IL-1β have been shown to be elevated in Alzheimer's disease (AD), and some studies show an association with disease progression [6; 7]. In APP/PS1 AD model mice, treatment with dapansutrile (7.5 g/kg chow or ~ 1000 mg/kg/d) for three months, starting at six months of age, when Aβ accumulation and neurological deficits are already present, reduced impairments in learning and

memory, based on Morris water maze performance [8]. This was accompanied by the restoration of synaptic plasticity, including long-term potentiation (LTP) induction and dendritic spine density. Treatment also reduced Aβ plaque load, and mitigated the neuroinflammatory response, including the pro-inflammatory cytokines IL-1β, IL-6, and TNFα. These effects may stem from the ability of dapansutrile to prevent the metabolic reprogramming of immune cells, such as microglia, toward a state of pro-inflammatory activation, in response to Aβ-related stress. Consistent with this hypothesis, dapansutrile treatment normalized the metabolic profile in the AD mice, which show evidence of mitochondrial dysfunction and altered fatty acid metabolism, based on plasma metabolomic analysis. These data suggest that dapansutrile is best suited toward the mitigation of inflammatory damage, thus it is likely to be most effective at the earliest stages of disease, to prevent neuronal damage, and may offer only marginal benefit once neuronal loss has occurred.

Spinal cord injury: POTENTIAL BENEFIT WITH EARLY INTERVENTION (Preclinical)
Levels of IL-1β and IL-18 in the CNS are very low under normal physiological conditions, but increase following injury due to the influx and activation of immune cells [9]. Levels of the downstream cytokine effectors of NLRP3 activation, IL-1β and IL-18 were found to be elevated following spinal cord injury in female mice [9]. At a dose of 200 mg/kg (i.p. once daily for 7 days) starting one-hour post-injury, mice treated with dapansutrile had greater preservation of hindlimb mobility, with 75% exhibiting stepping behavior, compared to 6% in the untreated group. This was accompanied by better survival of neurons in the injured region, as well as lower levels of active IL-1β and caspase-1. In response to the reduction in IL-1β, dapansutrile-treated mice also had lower infiltration of neutrophils and macrophages into the spinal cord, which may account for the mitigation of secondary damage to spinal cord neurons. Since these inflammation-related secondary damage processes begin within hours of the original injury, the timing of administration may be critical for therapeutic efficacy. However, since IL-18-related inflammation shows a delayed time course relative to IL-1β, later stage treatment may still offer some neuroprotective benefits.

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 [10]. 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 two-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. This is likely due to its effects on IL-1β, which is known to play a role in BBB permeability [11].

APOE4 interactions: Not known

Aging and related health concerns: Based on short clinical studies, it may reduce acute arthritis or gout-associated pain and inflammation. Benefits are most apparent when given prophylactically or at injury onset to prevent inflammatory damage.

Types of evidence:

- 4 clinical trials (2 Phase 2 RCTs for knee osteoarthritis n=79, n=202; 1 Phase 2 open-label trial in gouty arthritis n=29; 1 Phase 1b pilot trial in heart failure n=30).
- Several 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 two-week dose finding study (n=79, gel administered TID) (NCT01768975) and the six-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 [12]. However, these trials were completed in 2013 and 2015, respectively, and it is unclear, if the trials were positive, 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 [13]. The NLRP3 inflammasome

has been found to be in involved gout-associated inflammation, and IL-1 inhibitors are currently approved for the treatment of gout.

An oral formulation of dapansutrile has been tested in an open-label Phase 2a proof-of-concept study in patients with acute gout flares (n=29) (EudraCT Number: 2016-000943-14). Participants were treated with dapansutrile in a dose-adaptive manner (100 mg/day, 300 mg/day, 1000 mg/day, or 2000 mg/day) for eight days [14]. The co-primary endpoints were change in patient-reported target joint pain from baseline to day 3 and from baseline to day 7. The mean reductions in patient-reported joint pain were 52.4% ± 32.94%, 68.4% ± 34.29%, 55.8% ±44·90%, and 57.6% ± 38.72% at day 3, and 82.1% ± 22.68%, 84.2% ± 16.33%, 68.9% ± 34.89% and 83.9% ± 15.44% for the 100 mg/day, 300 mg/day, 1000 mg/day, and 2000 mg/day groups, respectively. General disability and walking disability also declined in all groups. Although there were no significant differences between groups, there was a dose-dependent decrease in investigator-assessed joint inflammation, with those in the 100 mg/day group showing only a marginal decrease in inflammation. Plasma IL-6 levels declined in all but the 100 mg/day group. There were no significant changes in plasma IL-1β, IL-18, or TNFα levels, but there was a significant reduction (44-45%) in *ex vivo* stimulation-induced IL-1β production in peripheral blood mononuclear cells (PBMCs) from patients in the higher dose groups. Without a placebo control, the magnitude of the effect is unclear. Larger studies are needed to determine whether dapansutrile offers clinically meaningful benefit in this population. An associated mechanistic study found that markers of inflammation, C-reactive protein (CRP) and serum amyloid A, were dose dependently decreased over the seven-day treatment course [16].

Dapansutrile (600 mg/kg) also reduced joint inflammation in a mouse model of gouty arthritis (monosodium urate injection), when administered prophylactically or one hour following the urate injection [13]. 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

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 [17]. Dapansutrile was tested in a randomized, double-blind Phase 1b trial (NCT03534297) at doses of 500, 1000, or 2000 mg/day (five oral capsules once, twice, or four times per day) for up to 14 days in patients with NYHA II–

III defined systolic heart failure (n=30) [18]. A placebo group was included to reduce bias, but the n's (n=2 per dosing cohort) were too small for statistical comparison. In the dapansutrile-pooled group, there was no significant change in systolic blood pressure over the 12±2 days of treatment, but a significant increase in systolic blood pressure in the placebo-pooled group. There were no significant changes in diastolic blood pressure or heart rate in either the dapansutrile or placebo groups. There was a significant decrease in fasting plasma glucose from baseline in the dapansutrile-pooled group (−10.5, 95% Confidence Interval [CI] −40 to 7 mg/dL). Although this trial was not powered to detect changes in functional parameters, an exploratory assessment of these measures is suggestive of benefit at the highest dose. There were improvements in left ventricular ejection fraction (from 31.5%, 95% CI 27.5 to 39%, to 36.5%, 95% CI 27.5 to 45%) and in exercise time (from 570, 95% CI 399.5 to 627 seconds to 616, 95% CI 446.5 to 688 seconds) in the dapansutrile 2000 mg cohort. There were no significant changes in quality-of-life measures (KCCQ and DASI scores), or systemic inflammatory markers (hsCRP or NT-proBNP). Overall, the results were consistent with what has been seen with IL-1 blockers in this population, and larger, controlled trials are needed to confirm clinical benefit.

In preclinical rodent models, IL-1β can induce a heart failure phenotype, and dapansutrile treatment has been shown to help preserve some aspects of cardiac function following myocardial injury. 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 [19]. 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 one 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. In male mice with severe ischemic cardiomyopathy due to non-reperfused anterior wall myocardial infarction, dapansutrile (7.5 g/kg chow for 9 weeks starting 7 days after injury) had no significant effect on left ventricle ejection fraction, but significantly increased preservation of their contractile reserve, which is a measure of β-adrenergic responsiveness [20].

Melanoma: POTENTIAL BENEFIT TO AUGMENT IMMUNOTHERAPIES (Preclinical)
Comparison of melanoma (n=469) and healthy skin samples (n=324) from the TCGA and GTEx cancer genome datasets revealed that the expression of NLRP3 and IL-β were higher in melanoma samples, and that levels of NLRP3 and IL-1β were highly correlated in the tumor tissue [21]. Tumor derived IL-1β stemming from NLRP3 activation was found promote an immunosuppressive tumor microenvironment

by inducing the expansion of myeloid-derived suppressor cells (MDSCs), and shifting the balance toward less cytotoxic CD8+ T cells and more immunosuppressive T regulatory cells [21]. Tumor progression was reduced in dapansutrile-treated mice implanted with B16F10 melanoma cells [21; 22]. The effect was driven by the effect on the immune system rather than on tumor cell proliferation, and was dependent on tumor driven IL-1β, as dapansutrile also inhibited tumor growth in NLRP3 deficient mice with NLRP3+ tumors [21]. MDSCs contribute to a variety of immunosuppressive mechanisms, including the expression of immune exhaustion markers PD-1/PD-L1. In mice, dapansutrile augmented the anti-tumor activity of anti-PD-1, suggesting it may be beneficial for overcoming anti-PD-1/PD-L1 resistance [21].

Colitis: UNLIKELY TO BENEFIT ESTABLISHED DISEASE (Preclinical)
Dapansutrile has been shown to protect against DSS-induced colitis in rodents when administered prophylactically, but not when administered therapeutically, after colon damage had been established [23]. When administered early, it reduced weight loss, histological damage, and pro-inflammatory cytokine levels (IL-1β, IL-6, TNFα) in the colon of mice. Notably, dapansutrile minimized the induction of NF-kB, the maturation of IL-1β, and activation of caspase-1 when administered prophylactically or therapeutically, but only showed disease activity benefit in the context of the former. A separate study in rats also found that prophylactic treatment reduced immune cell infiltration and histopathological damage to the colon, but as a monotherapy had limited impact on oxidative stress [23]. This suggests that in the context of chronic colitis, dapansutrile may help limit the induction of further inflammatory damage, but would need to be used in combination with other strategies that could ameliorate the pre-existing damage and/or dampen the ongoing damage-inducing cascades.

Asthma: POTENTIAL BENEFIT (Preclinical)
Dapansutrile (60 mg/kg i.p. or 7.5 g/kg chow) mitigated the eosinophilic asthma endotype in multiple mouse models of asthma [24]. The reduction in airway inflammation was linked to the reduced infiltration of eosinophils and neutrophils into the lungs. Consistent with its mechanism of action, treatment decreased NLRP3 expression and caspase-1 activation in lung tissue, and levels of activated IL-1β in broncho-alveolar lavage fluid. Dapansutrile appears most likely to be beneficial in protecting against acute exacerbations when used prophylactically.

Acute kidney injury: POTENTIAL MINOR BENEFIT (Preclinical)
When administered either prophylactically (prior to injury) or therapeutically (starting day of injury) dapansutrile (0.2 mg/kg i.p.) protected against folic acid-induced nephrotoxicity in male rats [25]. Kidney

function was partially preserved, though still impaired relative to control animals, based on serum creatinine and urea levels. This was accompanied by significant reductions in IL-1β, IL-18, and caspase-1.

Safety: Not associated with adverse events in acute studies, but long-term studies with chronic dosing have not been conducted. There is a 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, one Phase 1b in heart failure n=30)
- Several laboratory studies

Dapansutrile has been tested in six clinical trials (three for a topical formulation, and three for an oral capsule formulation), and according to the information disclosed by Olatec Therapeutics, was found to exert a good safety profile. No treatment-emergent serious adverse events have been reported. In the Phase 1 study of the oral capsules in healthy adults (n=35), [2] 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 eight days.
In patients with acute gout flares (n=29), there were no reported metabolic, physiological, or hematological changes, and all tested doses (up to 2000 mg/day for 8 days) were well-tolerated [14; 15]. The treatment-emergent adverse events were largely classified as metabolism and nutrition disorders (decreased appetite and hyponatremia) and gastrointestinal disorders (constipation, diarrhea, nausea), however the majority of the former were related to gout flares, rather than the study drug.
In patients with NYHA II–III systolic heart failure (n=30), there were no clinically significant changes in chemistry and hematology laboratory parameters, including albumin, total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, lipase, blood urea nitrogen (BUN), creatinine, cystatin C, sodium, potassium, calcium, chloride, hematocrit, hemoglobin, red blood cell and white blood cell count with differential, and glycated hemoglobin (HbA1c) for all tested doses (up to 2000 mg/day for up to 14 days) [18]. The most common adverse events were an increase in lipase levels (3/8 at the 500 mg dose), and diarrhea (4/8 at the 2000 mg dose). There were also no clinically relevant impacts to blood pressure, heart rate, or renal function, consistent with a good safety profile in this population.

In a preclinical study, treatment with dapansutrile (up to ~1000 mg/kg/day) for three months did not have any significant effects on basal synaptic transmission, synaptic plasticity (LTP), dendritic spine density, or performance on a task of spatial learning and memory (Morris water maze) in wild type (C57BL/6J) mice [8]. This suggests that, at least in the CNS, the therapeutic dosing range is likely to be wide enough to be compatible with clinical use.

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 [15], 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 (capsules) dapansutrile was found to be safe for acute administration up to eight 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]. In patients with gout or heart failure, dapansutrile was well-tolerated at oral doses up to 2000 mg/day for 8 to 14 days.

Research underway:

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

Dapansutrile is being tested in a randomized, double-blind, placebo-controlled Phase 2 trial for Covid-19 with cytokine release syndrome. The estimated completion date is in July 2022 (NCT04540120).

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 early 2023 (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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