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.

Pomaglumetad methionil (also known as POMA, LY-2140023)

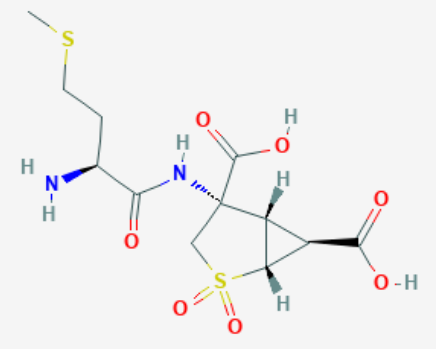
Evidence Summary

POMA has been tested for schizophrenia. Based on its mechanism of action, neuroprotective effects through mGluR3 activation may be offset by neurodegenerative effects through mGluR2 activation.

Neuroprotective Benefit: No studies have tested POMA for dementia or age-related cognitive decline. POMA activates both mGluR2 and mGluR3, which promotes neurodegeneration and neuroprotection, respectively.

Aging and related health concerns: No studies have examined POMA for treating or preventing age-related diseases.

Safety: Adverse events such as nausea, vomiting, headache, and insomnia are common. Due to POMA's mechanism of action, weight gain, extrapyramidal symptoms, and metabolic side effects common in dopaminergic antipsychotics may be avoided.

Availability: not available.	**Dose**: Oral doses of 40-80 mg BID have been tested in schizophrenia patients.	**Chemical formula:** $C_{12}H_{18}N_2O_7S_2$ **MW**: 366.4  Source: PubChem
Company: Eli Lilly; POMA has since been licensed to Denovo Biopharma		
Half life: not documented	**BBB**: not documented	
Clinical trials: Multiple phase 2-3 trials have tested POMA in 600-1000+ patients with schizophrenia.	**Observational studies**: none	

What is it? Pomaglumetad (also known as LY-404039) is a selective agonist for the metabotropic glutamate receptor subtypes mGluR2 and mGluR3. It modulates glutamatergic activity and reduces presynaptic release of glutamate at synapses. Pomaglumetad was being developed by Eli Lilly as a treatment for schizophrenia, anxiety disorders, and psychotic disorders. However, pomaglumetad had low absorption and bioavailability. Thus, a methionine prodrug of pomaglumetad, pomaglumetad methionil (also known as POMA or LY-2140023), was developed and tested for schizophrenia. In 2012, however, Eli Lilly announced the decision to stop ongoing phase 3 clinical studies testing POMA for the treatment of schizophrenia after a futility analysis concluded that the two pivotal studies were unlikely to be positive (Lilly Investors news). But in 2020, these drugs were tested at higher doses and the investigators concluded that the prior negative results from Lilly's phase 3 trials may have been due to inadequate doses (Kantrowitz et al., 2020). Since then, Denovo Biopharma exclusively licensed POMA from Eli Lilly to develop POMA for a subset of schizophrenia patients based on genetic biomarkers (PRnewswire).

Neuroprotective Benefit: No studies have tested POMA for dementia or age-related cognitive decline. POMA activates both mGluR2 and mGluR3, which promotes neurodegeneration and neuroprotection, respectively.

Types of evidence:

- Several clinical trials in schizophrenia patients
- 2 postmortem brain studies of mGluR2 and/or mGluR3 expression and distribution
- Several laboratory studies of the roles of mGluR2 or mGluR3

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:
None available.

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

The evidence for changes in mGluR2 and mGluR3 distributions with Alzheimer's disease is mixed. One study of postmortem brains reported that mGluR2/mGluR3 expression in the hippocampus and entorhinal cortex is decreased in the course of Alzheimer's disease and Lewy body dementia (Thorns et al., 1997). This study also showed colocalization of mGluR2/3 with amyloid precursor protein.

However, a different postmortem brain study reported that mGluR2 is expressed at low levels in pyramidal neurons in age-matched control cases, while much higher levels of mGluR2 expression are observed in Alzheimer's disease brains (Lee et al., 2004). This study also reported overlap between mGluR2 and neurofibrillary tangles (labeled with AT8).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
POMA is a selective agonist for mGluR2 and mGluR3. Mechanisms of action include modulation of glutamatergic activity and reduction of presynaptic glutamate release.

Schizophrenia: Several clinical trials have examined the efficacy of POMA in schizophrenia patients. In a phase 2 randomized open-label study of 261 schizophrenia patients, POMA treatment for 24 weeks resulted in improvement in the Positive and Negative Syndrome Scale (PANSS) total score, but improvement was significantly greater with the standard of care than POMA (Adams et al., 2013). In a large randomized controlled trial of 1,013 patients with schizophrenia, neither the low (40 mg BID) nor

the high dose (80 mg BID) of POMA for 6 weeks showed significant improvement compared to placebo on the PANSS total score (Downing et al., 2014).

In a phase 3 double-blind randomized controlled trial of 678 schizophrenia patients, POMA treatment (flexibly dosed between 20 and 80 mg BID) for 24 weeks showed significant improvement in the PANSS total score but this improvement was significantly less compared to aripiprazole, an antipsychotic medication (Adams et al., 2014). Similarly, the change in positive symptoms and general psychopathology symptoms for the aripiprazole treatment group was significantly greater than the change with POMA. There were no significant differences reported between POMA and aripiprazole groups in the improvement of negative symptoms (as measured by the PANSS negative scale and the NSA-16 scale).

However, POMA treatment resulted in significantly less weight gain than aripiprazole. Because of POMA's mechanism of action, it was not expected to be associated with weight gain, extrapyramidal symptoms, or metabolic side effects common in dopaminergic antipsychotic medications.

More recently, investigators hypothesized that the reason for POMA's failure in pivotal phase 3 trials was due to insufficient dosing and that higher doses were needed to engage the target (Kantrowitz et al., 2020). In a phase 1b study in 81 healthy volunteers, a high dose POMA treatment (320 mg/day) for 10 days significantly reduced ketamine-induced symptoms (measured by Brief Psychiatric Rating Scale; BPRS). However, neither low (80 mg/day) nor high POMA dose (320 mg/day) significantly affected the primary outcome measure of target engagement (ketamine-induced dorsal anterior cingulate cortex pharmacoBOLD). In this study, high-dose POMA exerted significant effects on clinical symptoms, but not on target engagement, suggesting an even higher dose may be needed.

Models of Alzheimer's and cognitive decline: No studies have examined the efficacy of POMA in models or patients of Alzheimer's disease. However, several studies have examined the role of mGluR2 and mGluR3 in cognitive functions and Alzheimer's disease pathology.

Cognitive deficits in aging and Alzheimer's disease appear to be associated with insults to mGluR3, while reductions in mGluR2 activation may be protective (Jin et al., 2018). In rhesus monkeys, mGluR3 is expressed not only in astrocytes but also postsynaptically in spine synapses of the dorsolateral prefrontal cortex, a brain region important for working memory. This spine synapse expression of mGluR3 is positioned to strengthen synaptic connectivity. In contrast, mGluR2 is expressed predominantly presynaptically. An mGluR3 agonist enhanced neuronal firing during a working memory

task via inhibition of cAMP signaling, while the mGluR2 positive allosteric modulator (BINA) produced an inverted-U dose-response on neuronal firing and working memory performance. Thus, these studies suggest that selectively activating postsynaptic mGluR3 may be beneficial for cognitive functions, while agents that activate both mGluR2 and mGluR3 (like POMA) might have mixed effects.

Several *in vitro* studies have also examined the roles of mGluR2 and mGluR3 in Alzheimer's pathology. In mixed and pure neuronal cultures exposed to synthetic Aβ, mGluR2 positive allosteric modulator (LY566332) amplified Aβ-induced neurodegeneration, and this effect was prevented by the mGluR2/3 antagonist (LY341495)(Caraci et al., 2011). However, a dual mGluR2/3 agonist (LY379268) was neuroprotective in mixed cultures. This neuroprotection was absent in neurons grown with astrocytes lacking mGluR3, suggesting that the protection against Aβ neurotoxicity was mediated through glial mGluR3.

Studies that used rat primary microglia and cultured cerebellar granule neurons reported that stimulation of mGluR2 induced microglial mitochondrial depolarization, apoptosis, and TNF-α release, while inducing a neurotoxic microglial phenotype (Taylor et al., 2005).

APOE4 interactions: Unknown.

Aging and related health concerns: No studies have examined POMA for treating or preventing age-related diseases.

Types of evidence:

- None

Given that mGluR2 and mGluR3 are expressed exclusively in the brain, POMA is unlikely to have benefits in age-related peripheral diseases.

Safety: Adverse events such as nausea, vomiting, headache, and insomnia are common. Due to POMA's mechanism of action, weight gain, extrapyramidal symptoms, and metabolic side effects common in dopaminergic antipsychotics may be avoided.

Types of evidence:

- 5 clinical trials

In a phase 3 double-blind randomized controlled trial in 678 schizophrenia patients, POMA treatment for 24 weeks resulted in 8.2% of people experiencing severe adverse events and 16.2% of people discontinuing due to adverse events; these rates were significantly higher than patients receiving aripiprazole, an antipsychotic medication (Adams et al., 2014). The most common adverse event that led to discontinuation among POMA-treated and aripiprazole-treated patients were schizophrenia symptoms (POMA, 2.9%; aripiprazole, 1.2%). One death (suicide) was reported in the POMA group but this incident was judged by the investigator to not be treatment-related. During the open-label active treatment phase, 12 (4.4%) patients experienced at least 1 severe adverse event.

No statistically significant differences in the incidence of treatment-emergent adverse events, extrapyramidal symptoms, or suicidal ideation/behavior were noted between POMA and aripiprazole groups. A significantly larger percentage of POMA-treated than aripiprazole-treated patients reported 7% or greater loss of baseline body weight at endpoint (13.1% versus 3.2%; $p<0.001$) and at any time (15.6% versus 4.5%; $p<0.001$) during the double-blind active treatment phase.

Nausea was the most frequent treatment-emergent adverse event in this phase 3 trial; however, only 1.3% of all patients discontinued the study due to nausea (Adams et al., 2014). Significantly more POMA-treated patients reported nausea compared with aripiprazole-treated patients (19.2% versus 11.2%; $p=0.023$). Compared with POMA-treated patients, aripiprazole-treated patients reported more incidents of akathisia (i.e., muscle quivering; 7.5% versus 2.5%; $p=0.007$), dyspepsia (i.e., indigestion; 3.7% versus 1.0%; $p=0.027$), pyrexia (i.e., fever; 2.5% versus 0.4%; $p=0.032$), and nasal congestion (1.9% versus 0.2%; $p=0.045$). Headache (5.9%), nausea (5.6%), and insomnia (3.0%) were the most frequent treatment-emergent adverse event during the open-label phase.

There were no significant differences between POMA and aripiprazole groups in the incidence of treatment-emergent neurological exam findings, except abnormal gait, which was significantly higher in the aripiprazole treatment group (2.5%) compared to the POMA group (0.4%)(Adams et al., 2014).

There were no clinically relevant laboratory findings for the POMA group, and there were no clinically significant findings on vital signs or electrocardiograms for the POMA group compared with the aripiprazole group during the double-blind active treatment phase. Both treatment groups had significant within-group decreases in cholesterol and small but significant within-group increases in fasting glucose, but there were no significant differences between treatment groups. There was no significant change from baseline in triglycerides for either of the treatment groups.

Other clinical trials have also reported similar findings. In the phase 2 randomized open-label study of 261 schizophrenia patients, POMA (40 mg twice daily) for 24 weeks resulted in 23 patients (17.7%) discontinuing due to adverse events (Adams et al., 2013). Only 27% in the POMA group completed the open-label 24-week treatment. POMA-treated patients reported significantly more treatment-emergent adverse events such as vomiting, agitation, and dyspepsia, while those in the standard of care group reported significantly more akathisia and weight gain. In a large randomized controlled trial of 1,013 patients with schizophrenia, a total of 44 (4.4%) patients experienced at least 1 serious adverse event (Downing et al., 2014). The most frequently occurring severe adverse events were schizophrenia-related events, but there were no significant between-group differences in serious adverse events. One patient in the POMA 80-mg BID group died secondary to cocaine intoxication. The overall incidence of adverse events leading to study discontinuation was not significantly different between treatment groups: placebo (11.2%), POMA 40 mg BID (7.9%), POMA 80 mg BID (12.9%), and risperidone (8.5%).

One double-blind crossover trial that examined the effects of POMA on QT interval reported that a single supratherapeutic dose of 400 mg POMA did not prolong QT interval (Zhang et al., 2015).

In a phase 1b study in 81 healthy volunteers, a high dose POMA treatment (320 mg/day) for 10 days resulted in significant nausea and vomiting, especially during early dosing, necessitating a brief dose titration schedule (Kantrowitz et al., 2020). There were no serious treatment-emergent adverse events with high or low-dose (80 mg/day) POMA, and only 2 non-completers were withdrawn by the study investigators due to non-serious adverse events deemed unrelated to study treatment (1 case of concussion and 1 case of sinus tachycardia with atrial fibrillation secondary to vomiting).

Drug interactions: Drug interactions have not been extensively studied. Based on the mechanism of action, POMA is likely to interact with other drugs that target the glutamatergic system.

Sources and dosing: POMA was developed and tested for schizophrenia by Eli Lilly. However, in 2012, Eli Lilly announced the decision to stop ongoing phase 3 clinical studies testing POMA after a futility

analysis concluded that the two pivotal studies were unlikely to be positive (Lilly Investors news). Since then, Denovo Biopharma exclusively licensed POMA from Eli Lilly to develop it for a subset of schizophrenia patients based on genetic biomarkers (PRnewswire). Oral doses of 40-80 mg, twice daily, have been tested in schizophrenia patients (Adams et al., 2014).

Research underway: No clinical trials are currently testing POMA according to ClinicalTrials.gov. Of the 7 on record, 3 have been completed, 3 have been terminated, and 1 has been suspended.

Search terms: pomaglumetad, POMA, LY-404,039, LY-2140023, mGluR2, mGluR3

- Pubmed
- Google

Websites visited for pomaglumetad, POMA, LY-404,039, LY-2140023:

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