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.

Arimoclomol

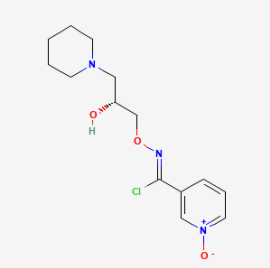
Evidence Summary

Arimoclomol is a co-inducer of molecular chaperones. It is approved for use in Niemann-Pick type C. Preclinical work suggests benefit in other diseases, but clinical evidence is limited.

Neuroprotective Benefit: Arimoclomol is approved for use in Niemann-Pick type C, but trials in ALS have failed to show efficacy. Preclinical evidence suggests potential use in other diseases with protein aggregation, but clinical evidence is needed.

Aging and related health concerns: Arimoclomol has largely not been explored for aging or related health concerns. One clinical trial of arimoclomol in inclusion body myositis failed to show efficacy.

Safety: Arimoclomol has been associated with upper respiratory infections, gastrointestinal complaints, and decreased weight. Other studies have reported increases in liver enzyme levels. Larger studies in more populations are needed to confirm safety profile.

Availability: Rx	**Dose**: Arimoclomol is an oral formulation. For approved indications, dosing is based on weight.	**Chemical formula:** $C_{14}H_{20}ClN_3O_3$ **MW**: 313.78 g/mol  Source: PubChem
Half-life: 4 hours	**BBB**: Penetrant	
Clinical trials: The largest clinical trial included 245 patients.	**Observational studies**: There are no observational studies of arimoclomol.	

What is it?

Lysosomal storage diseases are a heterogenous group of disorders that are all characterized by aberrant lysosomal function leading to excessive accumulation of a type of macromolecule in cells in various organ systems. The specific metabolic pathway that is disrupted and what organ system(s) is affected varies by disease (Rajkumar & Dumpa, 2023). Niemann-Pick Disease (NPD) is a rare inherited lysosomal storage disease. There are different subtypes of NPD, including Niemann-Pick type A, type B, and type C; these subtypes have different clinical characteristics stemming from different underlying genetic mutations and resulting mechanisms of action. Symptoms most often manifest in infancy or childhood, though some subtypes have a more diverse range of onset ages. Arimoclomol is the first approved treatment for Niemann-Pick disease type C (NPC), and is indicated for use along with miglustat, an FDA approved drug for another lysosomal storage disorder known as Gaucher's disease; miglustat is often used off-label in patients with NPC in the US. Miglustat is approved for use in NPC in other countries (Geberhiwot et al., 2018; Tirelli et al., 2024)

Clinical presentation of NPC can range from a rapidly progressive and fatal disorder that onsets in infancy to a chronic neurodegenerative disease that onsets in adulthood. NPC is an autosomal recessive disorder that is caused by mutations in the *NPC1* or *NPC2* gene that code for the corresponding NPC1 and NPC2 proteins; the specific mutation can influence the course of the disease. NPC1 and NPC2 are involved in the cellular trafficking of sterols. Reduction or loss of function of NPC1 and/or NPC2

interrupts this trafficking and results in excessive build-up of cholesterol in lysosomes (Geberhiwot et al., 2018; Rajkumar & Dumpa, 2023; Tirelli et al., 2024). Arimoclomol is a co-inducer of the heat shock response, a stress response mechanism that involves production of heat shock proteins (HSPs) that can act as molecular chaperones that promote proper protein folding and thus lysosomal function, among other potential roles (Kieran et al., 2004). In NPC, arimoclomol is thought to promote the physiological folding and acting of NPC1 and/or NPC2 and thus help restore their function (Mengel et al., 2021). Enhancing the heat shock response and thus levels of molecular chaperones may also have utility in a variety of diseases that are characterized by aberrant protein folding.

Neuroprotective Benefit: Arimoclomol is approved for use in Niemann-Pick type C, but trials in ALS have failed to show efficacy. Preclinical evidence suggests potential use in other diseases with protein aggregation, but clinical evidence is needed.

Types of evidence:

- 4 clinical trials
- 1 observational study
- 2 professional resources such as clinical management guidelines
- 1 press release
- 6 reviews
- 5 laboratory studies

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

Arimoclomol has not yet been studied for prevention of dementia or for its effects on cognitive function in healthy adults.

Human research to suggest benefits to patients with dementia:

Arimoclomol is approved for use in Niemann-Pick disease type C (NPC).

A randomized controlled phase 2/3 trial assessed the efficacy of arimoclomol compared to placebo in 50 pediatric patients with NPC; the trial lasted for 12 months. Patients continued to receive routine clinical

care, including miglustat, a drug approved for Gaucher's disease that is used off-label for NPC in the US. At the first visit, patients underwent a single dose pharmacokinetic (PK) study to confirm acceptable drug exposure; patients randomized to arimoclomol then received a dose that was scaled to be equivalent to 372 mg per day for adults with a body weight of 70 kg. Study drug was given three times a day by mouth. A total of 34 patients received arimoclomol and 16 received placebo. Patients who received arimoclomol had a 65% relative reduction in disease progression over the course of the year of treatment as measured by an NPC disease scale; there was a significant treatment effect in favor of arimoclomol (−1.40; 95% CI −2.76 to −0.03; p=0.046). In a secondary outcome measure, there was a higher proportion of patients who were stable or improved in the arimoclomol group compared to placebo (50% vs. 37.5%, respectively). In a prespecified subgroup analysis of patients on concomitant miglustat therapy, they found that patients who also received arimoclomol experienced disease stabilization, whereas patients who received placebo experienced disease worsening; the difference was statistically significant (mean change from baseline -0.06; 95% CI -0.90 to 0.78 in arimoclomol, mean change from baseline -2.06; 95% CI -3.49 to -0.63 in placebo, p=0.006). The study also examined biomarkers; in the arimoclomol group, there was a significant increase from baseline in Hsp70 level after 12 months of treatment with arimoclomol. The placebo group could not be analyzed, due to loss of samples. There was a significant reduction in levels of plasma Lyso-SM-509, a biomarker of NPC, in the arimoclomol group compared to the placebo group at the end of the trial (Mengel et al., 2021).

Participants in the above study were eligible to participate in a 4-year open label extension study, and Zevra Therapeutics also has an early access program for any qualifying patients with NPC in the US. The results from these two studies have not been published in a peer-reviewed journal but have been presented at conferences. The results were also submitted to the FDA and considered in the approval process. In September 2024, Zevra Therapeutics presented a series of posters at the Society for Study of Inborn Errors of Metabolism Annual Symposium. The data presented indicates that patients in the open-label study as well as patients in the early access program experienced disease stabilization rather than the expected disease progression. For instance, in the open-label extension, the researchers compared the disease progression in patients who had received placebo treatment and then switched to arimoclomol. During placebo treatment, the patients had an annual rate of change of 1.9 points on an NPC disease progression scale where higher numbers indicate worse disease; in the first year of arimoclomol treatment, the annual rate of change was 0.3 points (Zevra Therapeutics).

News articles about the approval of arimoclomol indicate that while the FDA voted to approve this application after rejecting a prior application for arimoclomol, that some of the committee members felt

the data indicated a 'slightly positive' effect rather than large effect size of arimoclomol, and that the staggering unmet need of NPC was a large factor in the decision (Fierce Pharma).

Arimoclomol has been tested in other diseases such as amyotrophic lateral sclerosis (ALS). A 6-month, 69 patient open-label extension after a safety and tolerability study of 84 patients with ALS found that disease progression was slower in the open-label participants compared to historical control groups, after controlling for baseline disease severity (Cudkowicz et al., 2008).

A small randomized controlled trial assessed the safety and efficacy of arimoclomol in 38 patients with ALS with mutations in the *SOD1* gene – a subpopulation with rapid rate of disease progression that is more homogenous than recruiting all patients with ALS. Additionally, mutations in *SOD1* in ALS render the SOD1 protein more prone to aggregation, and arimoclomol is thought to promote proper protein folding. The trial randomized patients to either placebo or 200 mg of arimoclomol three times daily. The study found no statistically significant efficacy results, though several assessments trended towards benefit of arimoclomol. When adjusting for severity of disease at baseline, the researchers found that there were numerically more patients in the arimoclomol group who were alive and had not yet required permanently assisted ventilation or a tracheostomy compared to placebo; this lower risk of diminished respiratory function or death trended towards but did not reach significance (HR=0.77; 95% CI 0.32 to 1.80). There was also a trend towards slower decline on a measure of ALS disease progression and forced expiratory volume (Benatar et al., 2018).

Based on the above results, a phase 3 study randomized 245 patients with ALS to either placebo or 400 mg arimoclomol three times daily for 76 weeks. There were no significant efficacy effects of arimoclomol; there was no difference in time to permanent assisted ventilation or death, or any other clinically meaningful effect. There was a significantly greater increase in serum neurofilament light chain levels in the arimoclomol group compared to the placebo group over the course of the trial. There was a numerical but not statistically significant increase in serum Hsp70 levels in the arimoclomol group compared to placebo; however, given the safety profile, a higher dose would not have been tolerated. The author state that the combined data indicate that at this dose, arimoclomol is 'not effective in modifying the progression of amyotrophic lateral sclerosis' (Benatar et al., 2024).

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

Heat shock proteins (HSP) are molecular chaperones; that is, they assist in and promote the proper folding of new proteins under physiological conditions, as well as the proper re-folding of misfolded proteins under stress conditions through preventing aggregation of unfolded proteins and even refolding aggregated protein. While they are called heat shock proteins and are part of the stress response pathway known as heat shock response, the pathway isn't activated by heat itself but rather by the presence of unfolded proteins that can result from heat or a variety of other stressors. The presence of unfolded proteins releases heat shock transcription factor one (HSF1) to migrate to the nucleus and lead to increased transcription of HSP genes (Richter et al., 2010; Turturici et al., 2011). Activating the heat shock response and inducing heat shock protein expression is therefore of interest to several fields, including neurodegenerative diseases, which are often characterized by protein aggregation. Besides for the chaperone activity, HSPs may have other neuroprotective mechanisms of action, such as inhibiting apoptosis, modulating inflammation, and improving lysosomal function (Turturici et al., 2011; Kim et al., 2020v; Mengel et al., 2021).

Arimoclomol is a co-inducer of the heat shock response; arimoclomol enhances the activation of HSF1 and therefore increases levels of HSPs such as Hsp70 (Kieran et al., 2004). Arimoclomol therefore should only increase HSP levels when there is a stressor such as unfolded or aggregated proteins, rather than acting as a cell stressor to activate the heat shock response (Turturici et al., 2011).

While the clinical trials to date that involve arimoclomol largely focus on patients with NPC or ALS, preclinical work in a variety of model organisms have suggested that increasing levels of HSPs could be beneficial for stroke, AD, Parkinson's disease (PD), and Huntington's disease (HD), among other neurodegenerative diseases (Turturici et al., 2011; Hunt et al., 2019; Kim et al., 2020). A 2024 study tested arimoclomol in a *C. elegans* model of tau toxicity; the disease model shows deficits in both motility and overall lifespan. Treatment with arimoclomol significantly improved motility and extended lifespan (Stanley et al., 2024). More work is needed in this area. While arimoclomol was reported to improve cognition in an ALS mouse model (Pelaez et al., 2024) and a rat model of hypoxia (Xu et al., 2011), it remains to be seen if and how arimoclomol affect cognition in AD models or other dementia models, or in humans.

APOE4 interactions:

It is not known whether there is any interaction between APOE4 status and arimoclomol.

Aging and related health concerns: Arimoclomol has largely not been explored for aging or related health concerns. One clinical trial or arimoclomol in inclusion body myositis failed to show efficacy.

Types of evidence:

- 1 clinical trial
- 1 observational study
- 3 reviews

Arimoclomol has mostly been studied in the context of neurodegenerative diseases. Its potential impact on aging and related health concerns is largely not known.

Arimoclomol has been tested in inclusion body myositis, a progressive muscle wasting disease that tends to onset after 50 years of age. The study randomized 152 patients with inclusion body myositis to either 400 mg of arimoclomol three times daily or matching placebo for 20 months. However, the study found that arimoclomol treatment was not efficacious for this disease (Machado et al., 2023).

Theoretically, arimoclomol or other modulators of the heat shock response could play a role in aging or longevity, as the aging process can involve an accumulation of cellular damage that chaperones could help to mitigate. This is a relatively unexplored area of the field, and likely influenced by confounding factors. For instance, low levels of chaperones could be associated with a low level of cellular stress and thus indicate a beneficial situation, or low levels of chaperones could indicate an impaired response to cellular stress, which could be deleterious (Murshid et al., 2013; Gomez, 2021). Future work may explore the effects of modulating heat shock protein levels in aging.

Safety: Arimoclomol has been associated with upper respiratory infections, gastrointestinal complaints, and decreased weight. Other studies have reported increases in liver enzyme levels. Larger studies in more populations are needed to confirm safety profile.

Types of evidence:

- 5 clinical trials
- 1 press release
- 2 professional resources such as the FDA label

Arimoclomol has been associated with upper respiratory tract infections, diarrhea, and decreased weight (FDA). Not all studies find increased instances of these events or have reported increased frequency of other events such as dizziness, decreased appetite, gastrointestinal complaints, rash, headache, or increased liver enzyme or creatinine levels; the differences may be due to different patient populations or relatively small trials (Benetar et al, 2018; Machado et al., 2023).

In a randomized controlled trial of 50 pediatric patients with NPC, there were more treatment-emergent adverse events in the arimoclomol group compared to placebo (88.2% vs. 75%, respectively), but fewer serious treatment-emergent adverse events in the arimoclomol group compared to placebo (14.7% vs. 31.3%, respectively). Two adverse events occurred more frequently in patients receiving arimoclomol compared to placebo: upper respiratory infection (17.6% vs. 6.3%, respectively) and decreased weight (14.7% vs. 0%, respectively). Vomiting and diarrhea were the most common adverse events in both the arimoclomol and placebo groups (23.5% and 25%, and 20.6% and 18.8%, respectively). There was one death; the patient was assigned to the arimoclomol group, and the death was considered to be related to NPC and not to the study drug. There were more study discontinuations due to adverse events in the arimoclomol group compared to placebo (8.8% vs. 0%); these adverse events included urticaria and angioedema, which were considered possibly related to study drug, and increased blood creatinine levels, which was considered probably study drug related. In total, 6 patients in the arimoclomol group had increase in serum creatinine. There were no other indications of effects on kidney function. There were no significant differences in vital signs, ECGs, or other laboratory values (Mengel et al., 2021).

An up to 4-year long open label extension study of the above trial, as well as data from an early access program, reported that there were no new safety signals (Zevra Therapeutics).

Three studies have tested arimoclomol in amyotrophic lateral sclerosis (ALS) patients. The first was a safety, tolerability, and pharmacokinetic study in 84 patients with ALS. Patients were randomized to three doses a day of either placebo or 25 mg, 50 mg, or 100 mg of arimoclomol. The randomized controlled trial lasted for 12 weeks; after that, patients could choose to enter a 6-month open-label extension protocol where they would receive 100 mg arimoclomol three times a day; 69 patients of the original 84 opted to enter this extension phase. No adverse events were significantly more common in the arimoclomol group than placebo. There were 9 serious adverse events, all considered to be unlikely or not related to study medication. There were two cases of pulmonary embolism in the 300 mg per day group during the randomized phase, and one case of pulmonary embolism during the open-label extension phase, though these were considered to be no more than possibly related to study drug (Cudkowicz et al., 2008).

A study of 38 patients with ALS tested 200 mg of arimoclomol three times daily to placebo. Most adverse events were mild, similar between groups, and not considered related to study drug. There were 22 total serious adverse events (15 in placebo, 7 in arimoclomol); none were considered to be related to study drug. One participant discontinued arimoclomol due to skin rash; this adverse event was considered to be probably related to study drug (Benetar et al, 2018).

A phase 3 study of 245 patients with ALS randomized patients to either placebo or 400 mg arimoclomol three times daily. There were more treatment-related adverse events in the arimoclomol group compared to placebo (p=0.052) and more participants experienced adverse events that lead to treatment discontinuation in the arimoclomol group compared to placebo (respectively 16% vs 5%, p=0.015). The most common adverse event leading to treatment discontinuation was increased liver enzymes; these were observed in 16 patients receiving arimoclomol, and no patients receiving placebo. The liver enzyme levels returned to normal upon treatment discontinuation. There was no difference in serious or severe adverse events, or in fatalities. The most common adverse events were more common in the arimoclomol group, and included gastrointestinal events (constipation, vomiting) and insomnia (Benatar et al., 2024).

A trial of arimoclomol in patients with inclusion body myositis tested 400 mg of arimoclomol three times daily against matching placebo during a 20-month treatment duration. In the 151 individuals included in safety analyses, the study found that a higher proportion of patients in the arimoclomol group had any adverse events (99%) compared to placebo group (90%); this increase was primarily in mild adverse events, as the incidence of moderate and severe adverse events were similar between the groups. Two

participants in the arimoclomol group experienced severe syncope compared to none in the placebo group. A higher proportion of arimoclomol patients discontinued treatment due to adverse events compared to placebo group patients (18% vs. 5%, respectively). There were two deaths, one in each group; they were not considered to be related to study drug. Decreased appetite, increased liver enzyme levels, and increased serum creatinine levels, were all observed numerically more frequently in the arimoclomol group. Increased alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels three or more times the upper limit of normal were reported in 5 arimoclomol patients and 1 in the placebo group; this led to study discontinuation for 4 of 5 of the arimoclomol group participants with this elevation. At least one more patient in the arimoclomol group and two more in the placebo group had increased ALT levels that were less than three times the upper limit of normal. Gastrointestinal complaints, headache, dizziness, altered body sensation, rash, redness, fatigue, and edema were also reported numerically more often in the arimoclomol group compared to placebo (Machado et al., 2023).

Drug interactions:

Arimoclomol is an inhibitor of the organic cationic transporter 2 (OCT2); as such, it may affect the pharmacokinetics of drugs that are substrates of OCT2. If a patient is receiving a drug that is an OCT2 substrate, patients should be monitored, and the dosage of the other drug should be decreased as needed. More specific drug interactions of arimoclomol are not currently available but will likely be better characterized as more patients use the medication and over longer periods of time.

Research underway:

NCT02612129 is a prospective randomized controlled trial of arimoclomol in patients with Nieman-Pick disease type C (NPC). The study enrolled 50 patients with NPC and randomized them to either arimoclomol or placebo; patients took their study drug orally three times daily for 12 months. Each patient underwent a single dose pharmacokinetic evaluation before the start of the study treatment period to determine the appropriate dose. Doses ranged between 31 and 125 mg arimoclomol. At the end of the 12-month randomized controlled period, patients could enter an open label extension phase when every patient would receive arimoclomol for up to 60 months. The primary outcome measure was change from baseline in disease severity. The estimated completion date is January 2025.

Search terms:

Pubmed, Google: arimoclomol, heat shock protein

- Niemann-Pick disease, ALS, dementia, Alzheimer's, inclusion body myositis, aging, longevity

Websites visited for arimoclomol:

- Clinicaltrials.gov
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma: Arimoclomol; Miplyffa