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.

Mirodenafil

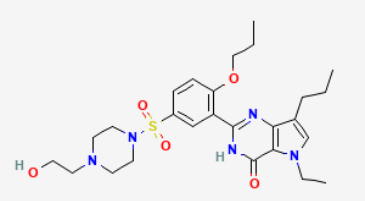
Evidence Summary

Mirodenafil has higher selectivity for PDE5 inhibition compared to other PDE5 inhibitors on the market. A phase 3 trial in early Alzheimer's patients is ongoing as of April 2024.

Neuroprotective Benefit: In a phase 2 study in Alzheimer's patients, mirodenafil treatment did not significantly affect primary endpoints, but post hoc analyses showed potential cognitive benefits in subgroups. Mirodenafil decreased plasma p-tau181 levels.

Aging and related health concerns: Mirodenafil is effective for the treatment of erectile dysfunction, including in people with other conditions such as diabetes and hypertension.

Safety: Mirodenafil is generally well-tolerated and adverse events are generally mild, including facial flushing and headache. Most studies of mirodenafil have been carried out in South Korea, so safety for other populations need to be studied further.

Availability: Rx in South Korea	**Dose**: Clinical trials in people with erectile dysfunction have tested mirodenafil doses of 50 or 100 mg, orally, on demand. The doses tested in Alzheimer's patients have been lower (10 or 30 mg/day of AR1001, orally).	**Chemical formula:** $C_{26}H_{37}N_5O_5S$ **MW**: 531.7  Source: PubChem
Half-life: 2.5 hours	**BBB**: penetrant	
Clinical trials: A meta-analysis of 3 randomized controlled trials included a total of 374 people with erectile dysfunction.	**Observational studies**: none available	

What is it?

Mirodenafil is a reversible selective second-generation phosphodiesterase 5 (PDE5) inhibitor. Inhibition of PDE5 suppresses cGMP hydrolysis in the cavernosal smooth muscle, resulting in smooth muscle relaxation and increased blood flow (Burnett, 2006). Mirodenafil was approved for the treatment of erectile dysfunction in South Korea in 2007. Mirodenafil has a 10-fold higher selectivity for PDE5 (IC50 of 0.34 nM) than sildenafil (IC50 of 3.5 nM), while having lower inhibitory effects on other PDEs (Park et al., 2014; Cho et al., 2016). An orally disintegrating film of mirodenafil became available in 2011 for patients who have difficulty swallowing tablets.

AR1001 (mirodenafil dihydrochloride) is under clinical development by AriBio Co., Ltd., a biopharmaceutical company based in South Korea, for the treatment of Alzheimer's disease. As of April 2024, a phase 3 trial in early Alzheimer's disease (named Polaris-AD) is ongoing in the US, South Korea, and the UK. AR1001 is also under development for the treatment of vascular dementia, dementia with Lewy bodies, and dementia with depression/PTSD.

For more information about first-generation PDE5 inhibitors (sildenafil, tadalafil, vardenafil, and others), please see the Cognitive Vitality Report on PDE5 inhibitors.

Neuroprotective Benefit: In a phase 2 study in Alzheimer's patients, mirodenafil treatment did not significantly affect primary endpoints, but post hoc analyses showed potential cognitive benefits in subgroups. Mirodenafil decreased plasma p-tau181 levels.

Types of evidence:

- Numerous clinical trials and observational studies of other PDE5 inhibitors
- One phase 2 study testing mirodenafil in Alzheimer's patients
- A few laboratory studies

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

No studies have tested whether mirodenafil prevents age-related cognitive decline or dementia. Observational research linking the use of other PDE5 inhibitors with lower risk of Alzheimer's disease, along with clinical trials testing the efficacies of tadalafil, sildenafil, udenafil, and vardenafil on cognitive function are described in the Cognitive Vitality Report on PDE5 inhibitors.

Human research to suggest benefits to patients with dementia:

In a phase 2 study of 210 patients with mild to moderate Alzheimer's disease, AR1001 treatment (10 or 30 mg daily, orally) for 26 weeks did not significantly affect the primary endpoints compared to placebo (change from baseline in ADAS-Cog13 and ADCS-CGIC)(Alzforum). However, a post hoc subgroup analysis hinted that patients taking 30 mg AR1001 alone, without concomitant treatment, might have improved on the cognitive scale (ADAS-Cog13). Also, a subgroup of milder patients, but not the moderate patients, showed improvement on ADAS-Cog13. Both the AR1001 10 mg dose and the 30 mg dose led to a decrease in plasma p-tau181, in contrast to an increase observed in the placebo group. A post hoc analysis suggested that in patients with the highest p-tau181 levels at baseline (most likely to be amyloid-positive), the AR1001 30 mg dose may have slowed decline on the ADAS-Cog13. Details of the results from this phase 2 trial have not been published in a peer-reviewed journal, as of April 2024.

A phase 3 double-blind randomized placebo-controlled trial (Polaris-AD) is ongoing as of April 2024, and is evaluating the efficacy and safety of AR1001 in people with early Alzheimer's disease (NCT05531526). For details of its study design, see the "Research Underway" section.

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

In rats, [14C]-mirodenafil treatment (40 mg/kg, orally) resulted in wide tissue distribution, including in the brain (Yoo et al., 2007). In the brain, radioactivity gradually increased with time up to 24 hours post-dose, suggesting that mirodenafil crosses the blood-brain barrier and acts on PDE5 in the cerebral blood vessels.

In a mouse model of Alzheimer's disease (APP-C105 mice), mirodenafil treatment (4 mg/kg, i.p.) for 4 weeks improved cognitive function measured by the Morris water maze and passive avoidance, while also reducing Aβ and phosphorylated tau (Kang et al., 2022). In the Morris water maze test, the APP-C105 transgenic mice treated with mirodenafil spent 64% less time and 44% less distance swimming to reach the target and spent 256% more time in the target quadrant compared to vehicle-treated APP-C105 mice. In cell culture studies, mirodenafil treatment increased levels of the nerve growth factor (NGF) and the neurotrophic factor BDNF. Mirodenafil treatment also increased neuronal survival by protecting the mitochondrial membrane potential and inhibiting apoptosis. Mirodenafil acted on many pathways: promoted neuronal survival through activation of the cGMP/PKG/CREB pathway, inhibited GSK-3β kinase activity (resulting in reduced tau phosphorylation), inhibited glucocorticoid receptor signaling, enhanced autophagic clearance (increased LC3B-II levels, a marker of autophagosome formation, and reduced levels of p62, a marker of phagocytic degradation), and activated Wnt/β-catenin signaling.

APOE4 interactions: Unknown

Aging and related health concerns: Mirodenafil is effective for the treatment of erectile dysfunction, including in people with other conditions such as diabetes and hypertension.

Types of evidence:

- 4 meta-analyses or systematic reviews
- 3 double-blind randomized controlled clinical trials
- 1 randomized controlled trial testing the oro-dispersible film formulation of mirodenafil
- Several reviews

Mirodenafil is approved for the treatment of erectile dysfunction in South Korea. It has been tested in people with erectile dysfunction with or without other comorbidities (e.g., diabetes, hypertension). Risk

factors for erectile dysfunction include diabetes mellitus, hypertension, cardiovascular diseases, cigarette smoking, nerve or spinal cord damage, psychological factors, and some medications (McMahon, 2019).

In a 2014 meta-analysis of 3 randomized controlled trials including a total of 374 people with erectile dysfunction, mirodenafil treatment (100 mg) for 12 weeks was more effective than placebo, as measured by the International Index of Erectile Function (IIEF) erectile function domain (EFD)($p<0.00001$ for both IIEF EFD score and change from baseline on IIEF EFD score compared to placebo)(Du et al., 2014). Mirodenafil treatment also significantly improved secondary outcomes, which were Sexual Encounter Profile (SEP) questions 2 and 3 and the response to Global Assessment Questionnaire (GAQ). All participants of the 3 trials were from South Korea.

In a phase 4 double-blind randomized controlled trial of 129 Korean men with erectile dysfunction, oro-dispersible film formulation of mirodenafil (50 mg or 100 mg, taken on demand) for 8 weeks significantly increased function, measured by IIEF-5, though only the 100 mg group showed a significant difference compared to placebo (Lee et al., 2022). Oro-dispersible mirodenafil also significantly improved SEP question 3, GAQ, and Life Satisfaction Checklist (LSC) compared with baseline.

In a 2021 network meta-analysis of 179 randomized controlled trials testing PDE5 inhibitors in people with erectile dysfunction, all PDE5 inhibitors were significantly more effective than placebo (Madeira et al., 2021). Sildenafil at the 25 mg dose was statistically superior to other PDE5 inhibitors in enhancing the IIEF, followed by sildenafil at 50 mg dose. The highest dose of mirodenafil (150 mg) was the treatment that caused more adverse events including flushing and headaches. Mirodenafil at the 100 mg dose and placebo were associated with discontinuation due to inefficacy. This meta-analysis suggested sildenafil at low doses (25 or 50 mg) followed by tadalafil (10 or 20 mg) as first therapeutic options for erectile dysfunction. The authors noted that the use of mirodenafil, avanafil, and lodenafil is not justified due to the lower efficacy and higher rates of adverse events. They noted that for people with cardiovascular disorders, low-dose sildenafil, vardenafil, and udenafil have the best benefit-to-risk profile.

In people with diabetes, the decrease in nitric oxide synthesis and the impaired activity of guanylyl cyclase restricts the production of cGMP, making erectile dysfunction more common and/or severe in this population (Fonseca et al., 2004). Treatment response to some PDE5 inhibitors can be lower in men with diabetes and erectile dysfunction compared to those without diabetes. In a 2019 Bayesian network meta-analysis of 15 randomized controlled trials with 5,274 patients with erectile dysfunction and

diabetes, vardenafil and mirodenafil had the highest probability of a positive response (measured by the Global Assessment Question positive response rate) compared to other PDE5 inhibitors (Liao et al., 2019). Mirodenafil had the highest probability of improving the Erectile Function Domain of International Index of Erectile Function (IIEF-EF) compared to other PDE5 inhibitors (sildenafil, tadalafil, vardenafil, udenafil, avanafil). The double-blind randomized controlled trial of 112 men with erectile dysfunction and diabetes reported that mirodenafil treatment (100 mg on demand) for 12 weeks significantly improved erectile function as measured by IIEF-EF, SEP, GAQ, and the LSC compared with placebo (Park et al., 2010). After 12 weeks of treatment, 32.7% of the mirodenafil group had an IIEF-EF score at or above 26, representative of normal erectile function, compared with only 9.4% in the placebo.

In a double-blind randomized controlled trial of 109 men with erectile dysfunction who were also taking antihypertensive medications, mirodenafil treatment (100 mg, as needed) for 12 weeks significantly improved erectile function as measured by a significantly greater increase in IIEF-EF scores compared to the placebo group (Paick et al., 2010). Participants treated with mirodenafil also showed greater improvement in secondary outcomes (other domains of IIEF, SEP3, LSC, and GAQ). After 12 weeks of treatment, 40.7% of the mirodenafil group had an IIEF-EF score at or above 26, representative of normal erectile function, compared with only 7.5% in the placebo ($p<0.001$).

In a systematic review of clinical trials in people with lower urinary tract symptoms secondary to benign prostatic hyperplasia, mirodenafil treatment significantly improved symptoms (Park et al., 2014). Larger, longer duration studies are needed to validate these findings.

Safety: Mirodenafil is generally well-tolerated and adverse events are generally mild, including facial flushing and headache. Most studies of mirodenafil have been carried out in South Korea, so safety for other populations need to be studied further.

Types of evidence:

- 4 meta-analyses or systematic reviews
- 1 randomized controlled trial testing the oro-dispersible film formulation of mirodenafil
- 2 randomized controlled trials in people with erectile dysfunction and other comorbidities
- 1 phase 2 study in people with Alzheimer's disease
- 2 reviews

Adverse events of PDE5 inhibitors are often related to the cross-inhibition of other PDEs (reviewed in Bischoff, 2004; Cho et al., 2016). For example, inhibition of PDE1 is related to adverse events such as flushing, tachycardia, and vasodilation. Inhibition of PDE3, which is expressed in cardiomyocytes, is associated with increased heart rate. Mirodenafil has a 254,000-fold selectivity for PDE5 inhibition over PDE3 inhibition, which is significantly greater than those of sildenafil, vardenafil, and tadalafil (selectivity of 4629-fold, 40,000-fold, and >4000-fold). PDE6 is exclusively expressed in the cones and rods of the retina and controls retinal cGMP levels. Thus PDE6 inhibition may cause visual disturbances such as blurred vision. Mirodenafil has a 30-fold selectivity for PDE5 inhibition over PDE6 inhibition, a few fold-greater than that of sildenafil (11-fold). There have been no visual adverse events reported in clinical studies of mirodenafil (Cho et al., 2016).

In a phase 2 study of 210 patients with mild to moderate Alzheimer's disease, AR1001 treatment (10 or 30 mg daily, orally) for 26 weeks was well-tolerated with a similar incidence of side effects and discontinuation in all groups (Alzforum). There was one death from COVID-19 and one participant on the 30 mg dose experienced a serious adverse event of fainting, which is possibly related to the drug. Details of specific adverse events and their incidences have not been published in a peer-reviewed journal as of April, 2024.

In a 2014 meta-analysis of 3 randomized controlled trials including a total of 374 people with erectile dysfunction, mirodenafil treatment (100 mg) for 12 weeks was associated with some drug-related adverse events such as flushing (15.8% in mirodenafil group vs 3.2% in placebo group) and headache (3.1% in mirodenafil group vs 0% in placebo group)(Du et al., 2014). Other adverse events included nausea and eye redness. All included trials noted that most adverse events were mild or moderate in severity, and no serious adverse events were reported during the study period. In one of the trials, a total of 4 participants, all from the mirodenafil 50 mg group, withdrew from the study due to mild to moderate adverse events (Paick et al., 2008).

Mirodenafil treatment has not had adverse effects on laboratory tests, electrocardiogram (ECG), or vital signs in men with erectile dysfunction, even in those with other conditions such as diabetes or in those who were taking concomitant medications such as antihypertensive medications or α1-blockers (Paick et al., 2008; Paick et al., 2010; Park et al., 2010; Lee et al., 2011; Bang et al., 2013). In a double-blind randomized controlled trial of 109 men with erectile dysfunction who were also taking antihypertensive medications, mirodenafil treatment (100 mg, as needed) for 12 weeks did not significantly change blood pressure, heart rate, electrocardiographic findings, or laboratory values, and did not significantly increase hypotensive symptoms (e.g., dizziness) (Paick et al., 2010). Facial flushing and headache were

the most common adverse events associated with mirodenafil, which were mild or moderate in severity, resolving spontaneously. There were no discontinuation of treatment due to adverse events and there were no serious treatment-associated adverse events. In a double-blind randomized controlled trial of 112 men with erectile dysfunction and diabetes, mirodenafil treatment (100 mg on demand) for 12 weeks did not significantly alter blood pressure, and most adverse events were mild in severity, with no serious adverse events (Park et al., 2010).

In a 2019 Bayesian network meta-analysis of 15 randomized controlled trials with 5,274 patients with erectile dysfunction and diabetes, treatment-related adverse events of PDE5 inhibitors (sildenafil, tadalafil, udenafil, vardenafil, mirodenafil, and avanafil) were generally mild (Liao et al., 2019). Adverse events with PDE5 inhibitors included headache, flushing, dyspepsia, respiratory tract disorder, distorted vision, dizziness, and nausea. Rates of adverse events across different PDE5 inhibitors were similar, except that they were significantly higher with sildenafil compared to vardenafil.

Mirodenafil has a 10-fold higher selectivity for PDE5 (IC50 of 0.34 nM) than sildenafil (IC50 of 3.5 nM), while having lower inhibitory effects on other PDEs, and therefore tolerability of mirodenafil is expected to be better than other PDE5 inhibitors (Cho et al., 2016). Accordingly, the overall incidence of treatment-related adverse events caused by mirodenafil (24.3-37.0%) is somewhat lower than those caused by sildenafil (45.0%), tadalafil (44.0%), and vardenafil (41.5%) (Tsertsvadze et al., 2009). There have not been any reports of serious cardiovascular events associated with mirodenafil, while sildenafil, tadalafil, and vardenafil have had 0.5%, 0.3%, and 0.2% incidences, respectively. Myalgia or back pain, which occurs in 4-5% of people taking tadalafil, has been very rare with mirodenafil. However, because there have not been head-to-head trials, and all subjects of mirodenafil trials have been from South Korea, further studies are needed to directly compare the safety profiles of these PDE5 inhibitors.

In a 2021 network meta-analysis of 179 randomized controlled trials testing PDE5 inhibitors in people with erectile dysfunction, mirodenafil at the highest dose (150 mg) was the treatment that caused more adverse events, especially flushing and headaches, compared to other PDE5 inhibitors (Madeira et al., 2021).

In a phase 4 double-blind randomized controlled trial of 129 Korean men with erectile dysfunction, oro-dispersible film formulation of mirodenafil (50 mg or 100 mg, taken on demand) for 8 weeks resulted in adverse events in 16.2% of participants in the 50 mg mirodenafil film group, 23.3% in the 100 mg mirodenafil film group, and 12.2% in the placebo group (Lee et al., 2022). Most treatment-associated adverse events were mild and resolved spontaneously. There were no serious adverse events.

Pharmacokinetics: The Tmax and half-life of mirodenafil are 1.25 and 2.5 hours, respectively (Park et al., 2014). Mirodenafil inhibits CYP3A4, CYP2C19, and CYP2D6 activities with IC50 values of 15.6, 38.2, and 77.0 µM, respectively.

Drug interactions: Intake of alcohol may delay the absorption of mirodenafil, but it may increase its bioavailability (Madeira et al., 2021). Mirodenafil treatment in people who are also taking antihypertensive medications did not significantly alter blood pressure, heart rate, electrocardiographic findings, or laboratory values, and did not significantly increase hypotensive symptoms (e.g., dizziness)(Paick et al., 2010). For information about drug interactions with first-generation PDE5 inhibitors (sildenafil, tadalafil, vardenafil, and others), see the Cognitive Vitality Report on PDE5 inhibitors.

Sources and dosing:

Mirodenafil, marketed as Mvix by SK Chemicals Life Sciences, is approved for the treatment of erectile dysfunction in South Korea. Clinical trials in people with erectile dysfunction have tested mirodenafil doses of 50 or 100 mg, orally, on demand (Paick et al., 2008; Du et al., 2014). The oro-dispersible film formulation of mirodenafil is available also at 50 mg and 100 mg doses (Lee et al., 2022).

AR1001 is under development for the treatment of Alzheimer's disease, vascular dementia, dementia with Lewy bodies, and mild cognitive impairment (AriBio company website). Clinical trials testing AR1001 in people with Alzheimer's disease have tested 10 and 30 mg daily doses, taken orally (NCT03625622; NCT05531526).

Research underway:

A phase 3 double-blind randomized placebo-controlled trial (Polaris-AD) is evaluating the efficacy and safety of AR1001 in people with early Alzheimer's disease (NCT05531526). The study is enrolling 1,150 participants and they will be randomized to receive AR1001 (30 mg daily, orally) or placebo for 52 weeks. AriBio is recruiting participants from 67 sites across the US, South Korea, and the UK (Alzheimer's News Today). The primary outcome is a change in Clinical Dementia Rating scale Sum of Boxes (CDR-SB) from baseline to 52 weeks (NCT05531526). Secondary outcomes include cognitive outcomes (ADAS-Cog13, MMSE), activities of daily living (Amsterdam-IADL), and geriatric depression scale. Other outcomes include safety (adverse events) and plasma/CSF biomarker levels. There is also a 2-year open-

label extension phase where all participants who choose to participate receive AR1001 (30 mg once daily) for 2 years. This study is estimated to be completed in December 2027.

Based on the AriBio company website, AR1001 is also in clinical testing for vascular dementia, dementia with Lewy bodies, and mild cognitive impairment (approved for phase 1 testing for all, as of April 2024).

Search terms:

Pubmed, Google: mirodenafil, AR1001, SK3530

Websites visited for mirodenafil:

- Clinicaltrials.gov (1)
- NIH RePORTER (0)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com (0)
- WebMD.com (0)
- PubChem
- DrugBank.ca
- Cafepharma (0)
- Pharmapro.com (0)