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.

Bardoxolone methyl

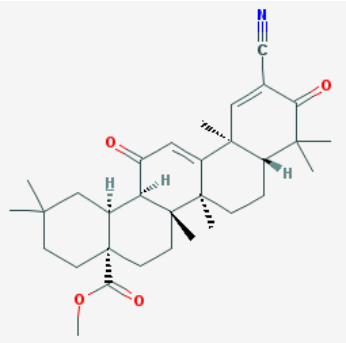
Evidence Summary

Most potential is in reducing risk of obesity-associated health problems and improving kidney function. Should be avoided by anyone with heart problems.

Neuroprotective Benefit: May protect against risk factors associated with cognitive decline, such as obesity, but no evidence for a direct effect. Limited BBB penetrance may mitigate therapeutic neuroprotective potential.

Aging and related health concerns: Weight-loss inducing agent in the overweight/obese that may be useful in mitigating poor diet-induced health problems. Also improves kidney function, and may be beneficial for hypertension and cancer.

Safety: Dangerous for individuals with a history of heart disease, otherwise moderately safe. The most common side effects are nausea, weight loss, and muscle spasms.

Availability: In clinical trials.	**Dose:** 20 mg/day for kidney disease, or 10 mg/day for hypertension as an oral capsule (clinical trials)	**Chemical formula:** $C_{32}H_{43}NO_4$ **MW:** 505.699 g/mol  Source: Pubchem
Half-life: Range 18-67 hours (median terminal elimination half-life 39 ± 9 hours)	**BBB:** Somewhat penetrant (less than other oleanane based synthetic triterpenoids)	
Clinical trials: 7 RCT Cancer: (Phase 1) Diabetes + Kidney disease: (Phase 2 & Phase 3 n=2185) Kidney disease: (Phase 2/3) Pulmonary hypertension: (Phase 2)	**Observational studies:** None	

What is it? Bardoxolone methyl (BARD, CDDO-ME, RTA-402) is an orally bioavailable semi-synthetic triterpenoid compound based of the scaffold of oleanolic acid. It was developed by Reata Pharmaceuticals as an activator of the Nrf2 antioxidant pathway. It has been tested in clinical trials for kidney disease, pulmonary hypertension, and cancer.

Neuroprotective Benefit: May protect against risk factors associated with cognitive decline, such as obesity, but no evidence for a direct effect. Limited BBB penetrance may mitigate therapeutic neuroprotective potential.

Types of evidence:

- 1 laboratory study

There have been no studies in humans examining the neuroprotective effects of BARD. There has been one preclinical study in rodents indicating that BARD treatment could prevent obesity associated cognitive decline, however, is probably due to its action in preventing obesity rather than a direct effect on cognitive function. It is likely to have less *in vivo* neuroprotective benefit than other similar compounds (RTA-405, RTA-408) since it has less blood brain barrier (BBB) penetrance.

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:

Obesity-associated cognitive decline: Potential benefit (mice)
In mice, pre-treatment with BARD (10 mg/kg/day) was able to prevent high-fat diet induced cognitive decline [1]. BARD prevented high-fat diet induced memory declines based on the novel object recognition task ($P<0.001$), as well as associated increases in glutamate NMDA receptor density ($P<0.05$), decreases in brain derived neurotrophic factor (BDNF) signaling ($P<0.05$), and increases in inflammatory mediators in the prefrontal cortex ($P<0.05$). These effects likely stem from the ability of BARD to interfere with the formation of the fat stores that send the cytokines and hormones which interfere with cognitive function. Whether BARD can reverse existing obesity-associated cognitive impairments or has any direct neuroprotective effects remains to be determined.

APOE4 interactions: Unknown

Aging and related health concerns: Weight-loss inducing agent in the overweight/obese that may be useful in mitigating poor diet-induced health problems. Also improves kidney function, and may be beneficial for hypertension and cancer.

Types of evidence:

- 7 clinical trials (2 Phase 1, 4 Phase 2, 1 Phase 3 RCT)
- Numerous laboratory studies

Kidney disease: Benefit
BARD has been tested most extensively for its potential ability to improve kidney function. The trials primarily use enhanced glomerular filtration rate (eGFR) to assess kidney function. Studies were initially performed in patients with Type 2 Diabetes and Stage 4 Kidney disease, however, the Phase 3 RCT (BEACON NCT01351675) in this population had to be terminated due to a significant increase in heart failure in the BARD treated patients [2]. In the Phase 2 RCT (BEAM NCT00811889), BARD treatment significantly increased eGFR compared with placebo at 24 weeks ($P<0.001$), and the increases were maintained through 52 weeks [3]. Post-hoc analyses from the Phase 3 BEACON trial indicated a similar improvement in eGFR ($P<0.001$) [2; 4]. In a subset analysis of patients from the LARIAT trial with baseline impaired kidney function, eGFR improvements were seen starting at 16

weeks (p<0.0001) and maintained for at least 2 years. BARD is currently being tested in the Phase 2/3 RCT (CARDINAL NCT03019185) for use in patients with Alport syndrome, which is a genetic disease involving progressive loss of kidney function. Interim results indicate increases in eGFR starting at 4 weeks and progressively improving for 12 weeks (P<0.00005), as well as decreases in other measures of kidney dysfunction (BUN, uric acid, and phosphorus). Retrospective analysis from a Phase 1 study in cancer patients also indicated improved eGFR all patients (P<0.0001) [5]. These results suggest that BARD is beneficial in improving kidney function in the context of various pathological conditions and may help protect against kidney damage.

Pulmonary Hypertension: Potential benefit

In the Phase 2 RCT (LARIAT NCT02036970) BARD (up to 10 mg daily) was tested for its ability to improve pulmonary arterial hypertension (PAH) in patients with interstitial lung disease. BARD treated patients had significantly improved performance on the primary outcome measure, the 6-minute walk test, which is indicative of improved lung function possibly due to decreased pulmonary blood pressure [6]. Phase 3 RCT (CATALYST NCT02657356) and long-term safety (RANGER NCT03068130) studies will clarify the true clinical benefit for PAH.

Cancer: Potential benefit

BARD treatment was shown to induce apoptosis, prevent the induction of inflammatory mediators, and potentiate the cytotoxic effect of chemotherapy agents in acute myeloid leukemia (AML) tumor cells [7]. It also decreased the viability of imatinib-resistant chronic myeloid leukemia (CML) cells through the induction of oxidative stress (depletion of glutathione and loss of mitochondrial membrane potential) [8]. In a mouse metastatic breast cancer (4T1) model, i.v. injection of BARD 1 day after tumor implant completely prevented tumor formation, whereas treatment starting 5 days later decreased tumor size approximately 10 fold (P<0.0001) [9].

BARD was tested in patients with advanced stage solid tumor cancers in a Phase I RCT (NCT00529438). Biopsied tumor cells expressed less inflammatory mediators, lower levels of cell cycle genes, and had increased DNA fragmentation, indicative of a shift toward less proliferation and more cell death [5]. Based on tumor size, 1 (out of 8) patient had a complete response, 1 had a partial response, while 10 had disease stabilization. However, the sponsor (Reata) chose to terminate Phase 2 trials for advanced melanoma and pancreatic cancer to pursue other indications. It is unclear whether BARD will continue to be developed as an anti-cancer therapeutic.

Obesity: Benefit

BARD has been demonstrated to prevent high-fat diet induced obesity in mice and to induce weight loss in overweight and obese individuals with Type 2 diabetes in clinical trials.

Weight loss was a noted side effect in the BEAM and BEACON clinical trials testing BARD in patients with Type 2 diabetes, and the CARDINAL trial in Alport patients. In BEAM, **patients experienced dose-dependent weight loss** [3]. Average weight loss was: 7.7 kg with 25 mg, 9.2 kg with 75 mg, and 10.1 kg with 150 mg (compared to 2.4 kg with placebo). Notably, there was only significant weight loss in overweight patients with a body mass index (BMI) ≥ 25. In the BEACON trial (20 mg dose), patients on BARD had a significant decrease in body weight (-5.7 kg vs placebo p<0.001), and significantly reduced waist circumference (Week 24: -4.1 ± 8.0 cm, Week 48: -6.5 ± 9.3 cm), especially in the obese (BMI >30). **Weight loss was proportional to initial BMI**, with weight plateauing at 32 weeks in the normal weight (BMI 18-24.9) group but continuing to decline for overweight patients (BMI 25+). This weight loss appears to be due to loss of fat rather than muscle mass. In the CARDINAL trial, average weight loss was 1kg per month. The future development for this purpose would have to be contingent upon a contraindication for individuals with a history of heart disease.

Rodent studies offer a potential mechanism for BARD induced weight-loss. In mice fed a high-fat diet, BARD treatment (10 mg/kg) prevented the accumulation of mesenteric fat and visceral fat, which is hypothesized to stem from the increased sympathetic system activity in the adipose tissue, while also reducing the level of proinflammatory macrophages in adipose tissue [10; 11]. BARD prevented fat accumulation and induced a shift in fatty acid metabolism genes in the liver toward more β-oxidation and less lipogenesis [12]. BARD treatment could also attenuate cardiac and renal hypertrophy and fat accumulation [13]. BARD was effective in preventing high-fat diet induced insulin resistance, and lowering fasting plasma triglycerides, free fatty acid levels, and fasting glucose levels, suggesting it could prevent diet-induced diabetes [12; 14]. Furthermore, BARD could prevent leptin-insensitively in the hypothalamus, which is beneficial in preventing overeating [15]. It should be noted that the majority these studies were done by a single lab group.

Safety: Dangerous for individuals with a history of heart disease, otherwise moderately safe. The most common side effects are nausea, weight loss, and muscle spasms.

Types of evidence:

- 7 clinical trials (2 Phase 1, 4 Phase 2, 1 Phase 3 RCT)
- Numerous laboratory studies

In most clinical trials there were no serious adverse events. The **most common adverse event (AE) across trials was nausea.** However, in the Phase 3 BEACON trial, there was a significant increase in heart failure.

In a Phase 1 study in cancer patients 82% experienced at least 1 drug related AE, 82% of which were grade 2 or less [5]. The most common AE were fatigue (40%), nausea (34%), and anorexia (30%). Side effects that may induce weight loss could potentially be problematic for cancer patients. In pulmonary hypertension patients, nausea was also the most common AE (39%) and emerged at the 20 mg dose [16].

In Phase 2 studies for patients with kidney disease, the most common AE was muscle spasms (42% at 25 mg dose) [3; 17].

In the Phase 3 BEACON trial, 96 patients taking BARD had heart-failure events vs 55 taking placebo (hazard ratio (HR): 1.83; 95% CI, 1.32 to 2.55; P<0.001) [2]. A total of 139 patients in the BARD group, as compared with 86 in the placebo group, had a composite outcome event of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death from cardiovascular causes (HR: 1.71; 95% CI, 1.31 to 2.24; P<0.001). Subsequent analysis revealed that the **increased incidence of heart failure was due to fluid overload.** Three risk factors have been identified to predict which patients are likely to have this serious AE. They include having stage 4 chronic kidney disease, prior heart failure, and elevated baseline B-type natriuretic peptide (BNP) [18]. As a result, subsequent trials have excluded patients with these risk factors and have not had problems with increased heart failure in treated patients.

Potential drug interactions are unknown.

Sources and dosing:

Bardoxolone methyl (BARD) was developed by Reata Pharmaceuticals and its use in clinical trials is being sponsored by both Reata and AbbVie. It was granted Orphan Drug Status by the FDA for Alport syndrome and pulmonary arterial hypertension and by the EMA for Alport syndrome. Clinically, BARD is only currently available to patients enrolled in clinical trials. BARD (CDDO-ME) can be purchased for research, but not patient use, through biological chemical suppliers.

The therapeutic dose established for use in trials of kidney disease is 20 mg/day as oral capsules. The crystalline preparation has been associated with less side effects than the amorphous spray dried dispersion formulation. The dose used in the pulmonary hypertension trials is 10 mg/day. 900 mg/day was set as the therapeutic dose for cancer [5].

Research underway:

There are currently 5 active recruiting clinical trials for BARD.

Kidney disease:

The Phase 3 part of the CARDINAL (NCT03019185) trial for Alport syndrome has an expected completion date of December 2020.

A Phase 2 trial (PHOENIX NCT03366337) for patients with rare chronic kidney disease is estimated to be completed in April 2019.

A new Phase 3 trial (AYAME NCT03550443) for patients with diabetic kidney disease has a projected completion date of March 2022.

Pulmonary hypertension:

A Phase 3 trial (CATALYST NCT02657356)) for patients with connective tissue disease-associated pulmonary arterial hypertension has an expected completion date of June 2020.

A Phase 3 long-term safety trial (RANGER NCT03068130) for patients with pulmonary hypertension is estimated to be completed in December 2020.

Search terms:

Pubmed, Google: Bardoxolone methyl + aging, neurodegeneration, cognitive, clinical trials, cancer, cardiovascular, diabetes, obesity, kidney, safety, meta-analysis,

Websites visited for Bardoxolone methyl:

- Clinicaltrials.gov
- PubChem
- DrugBank.ca

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