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.

AR1001

Evidence Summary

This PDE5 inhibitor may be better suited to CNS indications than currently approved drugs in this class. It is well tolerated. Larger studies are needed to determine clinical efficacy and long-term safety.

Neuroprotective Benefit: AR1001 may only benefit patients with very early-stage cognitive impairment. More comprehensive studies are needed to determine whether it can mitigate decline in a clinically meaningful manner, in this population.

Aging and related health concerns: AR1001 has not yet been tested in other aging-related diseases.

Safety: AR1001 was well-tolerated in a yearlong clinical trial in AD patients, though long-term safety has not been established. The side effect profile is likely to be influenced by its phosphodiesterase selectivity profile.

Availability: In clinical trials	**Dose**: Not established Tested at 10 mg and 30 mg once daily in the form of oral tablets	**Chemical formula:** Not published **MW**: Not published
Half-life: Not published	**BBB**: Penetrant	
Clinical trials: A Phase 2 RCT (n=210) in Alzheimer's disease has been completed.	**Observational studies**: None	

What is it?

AR1001 is a pyrrolo-pyrimidinone phosphodiesterase 5 (PDE5) inhibitor originally developed for erectile dysfunction, that is currently in clinical development for Alzheimer's disease. It is being developed by the South Korean biopharmaceutical company, Aribio Co. AR1001 is 10-fold more potent at inhibiting PDE5 relative to sildenafil, and has superior BBB penetrance.

Neuroprotective Benefit: AR1001 may only benefit patients with very early-stage cognitive impairment. More comprehensive studies are needed to determine whether it can mitigate decline in a clinically meaningful manner, in this population.

Types of evidence:

- 1 clinical trial in AD
- 1 laboratory study

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function: None specifically for AR1001, though there is evidence that PDE5-affected signaling pathways are altered in the context of dementia [1].

Human research to suggest benefits to patients with dementia:

AR1001 has been tested in a Phase 2 RCT in patients with mild to moderate Alzheimer's disease (AD) (MMSE 16-26) (n=210) (NCT03625622). The 26-week placebo-controlled study tested AR1001 at doses of 10 or 30 mg once per day, with an optional 26-week open label extension. Patients were able to stay on their stable doses of approved AD, thus some patients took AR1001 alone, while others used it

concomitantly with their other medication. The co-primary endpoints were changes in the ADAS-Cog13, which focuses on cognition, and ADAS-CGIC, which focuses on behavioral and functional changes, with respect to baseline. Secondary endpoints included other cognitive batteries, neuropsychiatric batteries, and quality of life measures.

The results were presented at CTAD 2021 [2]. At 26 weeks, there were no significant differences on any of the measures, relative to the placebo group. Since the original study was only 26 weeks, the 52-week data lack a placebo comparator group, so these measures are relative to baseline, and thus could be confounded by practice effects. On the ADAS-Cog13, there was a 1.17-point decline in the 10 mg group, and a 0.76-point decline in the 30 mg group at 52 weeks, relative to baseline (Press release). This level of decline is significantly lower than what has been reported as the average for placebo groups (5.5 points), based on a meta-analysis of prior studies in this patient population, however this historical control group may not be truly comparable to the participants in this study. Performance on the ADAS-CGIC was relatively stable across the groups over the course of the study, and there were no significant differences relative to placebo.

The potential protective effect was limited to patients with mild disease who were taking AR1001 alone (i.e., without other AD medications). Post-hoc analyses found that more than half of the , patients in this subgroup taking 10 mg or 30 mg AR1001 showed statistically significant improvement on the ADAS-Cog13. This was defined as greater than two points improvement, however, clinically meaningful improvement is typically considered to be at least four points, which may account for the lack of notable improvement on functional measures. Additionally, the n's are very small for these subgroup analyses. There was no evidence of benefit in patients with moderate disease. Similar trends were seen with secondary endpoints. The biomarker analysis has not yet been completed, so it is unclear whether these effects are accompanied by changes in AD biomarkers.

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

The publicly available preclinical evidence supporting the neuroprotective properties of AR1001 is limited to one poster presentation at AAIC 2020 [3]. As would be expected from a PDE5 inhibitor, AR1001 was associated with an increase cGMP levels and cGMP-dependent signaling cell survival pathways, such as the activation of CREB in neuronal cell culture. AR1001 also showed effects toward inhibiting Aβ accumulation. *In vitro*, AR1001 disrupted pre-formed Aβ fibrils, while in cell culture, it reduced the expression of amyloid precursor protein (APP), beta-site APP cleaving enzyme 1 (BACE1)

and Dickkopf-1 (Dkk1) through the downregulation of the glucocorticoid receptor. *In vivo*, AR1001 reduced Aβ plaque deposition in the 5XFAD AD mouse model, and improved performance on the Morris water maze and passive avoidance task in the NSE/APP-C105 AD mouse model.
APOE4 interactions: Not established

Aging and related health concerns: AR1001 has not yet been tested in other aging-related diseases.

Types of evidence:

- 0 meta-analyses or systematic reviews
- 0 clinical trials
- 0 observational studies
- 0 laboratory studies

There are no publicly available studies assessing AR1001 for aging-related diseases, though depending on its pharmacokinetic and pharmacodynamic profile, it might have similar effects, particularly with respect to vascular dynamics, with other PDE5 inhibitors.

Safety: AR1001 was well-tolerated in a yearlong clinical trial in AD patients, though long-term safety has not been established. The side effect profile is likely to be influenced by its phosphodiesterase selectivity profile.

Types of evidence:

- 1 clinical trial

Safety information from Phase 1 studies has not been made publicly available. In the Phase 2 RCT in AD patients, AR1001 was generally well-tolerated, with over 80% of patients in the original study choosing to continue into the open-label period [2]. The rate of adverse events and discontinuations due to adverse events was similar across treatment groups, with the highest rate in the placebo group. The adverse events were primarily mild or moderate. The most common adverse events overall were urinary tract infections (10.6%), diarrhea (7.1%), depression (6.4%), skin lacerations (5.7%), and headache (5%).

The selectivity profile of AR1001 for PDE5 relative to all of the other PDEs has not been disclosed, but is likely to be a key component of the side effect profile, as many of the major side effects for approved PDE5 inhibitors are related to off-target inhibition of other PDEs.

Drug interactions: Not established. AR1001 may show similar interactions as other PDE5 inhibitors, depending on its metabolic clearance. In the Phase 2 RCT, patients taking AR1001 with concomitant AD medications had worse outcomes than those taking AR1001 alone, suggesting there may be a negative interaction between these medications.

Sources and dosing:

AR1001 is currently only available in clinical trials. It is being developed for AD by Aribio Co. In a clinical trial for AD, it was dosed at 10 mg and 30mg.

Research underway:

According to the pipeline page of the Arbio website, Phase 1 clinical trials have also been conducted for AR1001 in the context of vascular dementia and mixed dementia. The pipeline also indicates development of AR1001 for ALS, although clinical studies have not yet been conducted in this population. A Phase 3 RCT for AR1001 in AD is planned for 2022 (Press release).

Search terms:
Pubmed, Google: AR1001

- Alzheimer's disease, clinical trial, safety

Websites visited for AR1001:

- Clinicaltrials.gov

References:

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2. Greely D, Scheltens P, Rock J *et al.* (2021) OC8 - Results of a Phase 2 Study of AR1001 in Mild to Moderate Alzheimer's disease Patients. *Oral Communications CTAD* https://www.ctad-alzheimer.com/files/files/CTAD21%20Oral%20communications.pdf

3. Kang BW, Kim F, Choi YP *et al.* (2020) AR1001 ameliorates Alzheimer's disease pathology and symptoms by multi-mechanisms. *Alzheimer's & Dementia* **16**, e047266.https://alz-journals.onlinelibrary.wiley.com/doi/abs/10.1002/alz.047266.