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.

ORM-12741

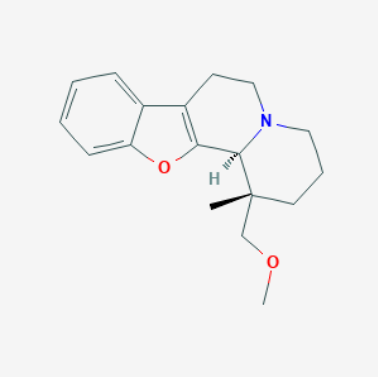
Evidence Summary

The first phase 2 trial in Alzheimer's showed benefits in some cognitive and behavioral (neuropsychiatric) measures but results from the larger phase 2 have not been made publicly available.

Neuroprotective Benefit: A phase 2 trial in Alzheimer's showed benefits in some cognitive and behavioral measures but results from the subsequent trial are not available. Treatment may improve symptoms but may not have disease-modifying effects.

Aging and related health concerns: No studies, clinical or preclinical, have evaluated the efficacy of ORM-12741 on age-related health conditions. ORM-12741 failed to improve symptoms in people with systemic sclerosis in a small phase 2a trial.

Safety: ORM-12741 has been well-tolerated in multiple phase 1 and 2 studies, though it is not clear how the drug affects organs (e.g., kidney, uterus, prostate) that express α2C-adrenoceptors at much higher levels compared to the brain.

Availability: not available; in clinical trials	**Dose**: The phase 2a trial in Alzheimer's patients tested two dose ranges: 30-60 mg/day or 100-200 mg/day.	**Chemical formula:** $C_{18}H_{23}NO_2$ **MW**: 285.4  Source: PubChem
Half life: unpublished	**BBB**: penetrant	
Clinical trials: The phase 2 trial in Alzheimer's patients enrolled 308 patients.	**Observational studies**: none	

What is it? ORM-12741 (also known as DB105) is a novel selective antagonist of α2C adrenoceptors. ORM-12741 was developed by Orion Corporation, but Denovo Biopharma LLC licensed it in June 2019, gaining global rights to develop, manufacture, and commercialize ORM-12741 for Alzheimer's disease (PR Newswire). The role of the α2C adrenergic receptor in Alzheimer's disease has not been explored extensively, though its role in modulating cognitive functions in schizophrenia is better-studied (AlzForum). Genetic polymorphism of the α2C adrenergic receptor is associated with dysfunction in major depressive disorder, attention deficit hyperactivity disorder, and schizophrenia (Uys et al., 2017). ORM-12741 was originally part of a schizophrenia drug discovery program, but it is no longer being developed for this indication after some early clinical studies in Europe. The highest densities of α2C adrenergic receptors in the brain are found in the ventral and dorsal striatum and in the hippocampus (Rinne et al., 2016). α2C adrenergic receptors may play an important role in the modulation of dopamine and serotonin neurotransmission in the brain. Behaviorally, α2C antagonists produce antidepressant and antipsychotic effects while improving learning and memory functions. Because α2A- and α2C- adrenergic receptors often have opposing CNS roles, and α2A adrenergic receptors represent 90% of α2 adrenergic receptors, subtype-specific targeting is gaining more interest for CNS indications (Uys et al., 2017).

Neuroprotective Benefit: A phase 2 trial in Alzheimer's showed benefits in some cognitive and behavioral measures but results from the subsequent trial are not available. Treatment may improve symptoms but may not have disease-modifying effects.

Types of evidence:

- 1 clinical trial
- 1 gene expression study
- Several laboratory studies

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:

Two clinical trials for Alzheimer's have been completed, though results from only the first one is publicly available.

The first Alzheimer's trial was a double-blind, randomized, placebo-controlled trial that enrolled 100 patients with Alzheimer's and neuropsychiatric symptoms (Rinne et al., 2016). Their primary outcome was CDR System Standard Composite Domain Factor scores: Quality of Episodic Memory, Quality of Working Memory, Power of Attention, and Speed of Memory Retrieval. A statistically significant treatment effect was seen in 1 of the 4 primary CDR system end points--Quality of Episodic Memory (p=0.030), favoring ORM-12741 over placebo. The Quality of Episodic Memory composite scores decreased from baseline to week 12 by a mean (SD) of 32.4 (50.6) points in the placebo group but increased by 4.6 (51.5) points in the low-dose group and also increased by 5.2 (42.5) points in the high-dose group. No clear differences between the two different ORM-12741 doses were observed.

The overall treatment effect was not statistically significant for the Quality of Working Memory composite score. The estimated treatment difference was 0.16 points (95% CI, 20.02 to 0.33, P=0.079) for the low dose versus placebo and 0.11 points (95% CI, 20.06 to 0.28, p=0.219) for the high dose versus placebo. The most marked difference between ORM-12741 and placebo was seen in the post hoc–calculated Quality of Memory composite score that combined all of the accuracy measures from the 6 tests included in the Quality of Episodic and Working Memory composite scores. The overall treatment effect was statistically significant (p=0.013) over the 12 weeks of treatment, with subjects in

both ORM-12741 dose groups improving on Quality of Memory and subjects on placebo showing a steady decline. The estimated treatment difference was 37.4 points (95% CI, 10.9–63.9, p=0.006) for the low dose versus placebo and 31.1 points (95% CI, 5.19 to 57.1, p=0.019) for the high dose versus placebo. The effect size was 1.54 for the low dose versus placebo and 1.12 for the high dose versus placebo at 12 weeks. No statistically significant treatment effect was detected in the other composite cognitive domain scores of Speed of Memory, Power of Attention, or Continuity of Attention.

Neuropsychiatric Inventory (NPI) caregiver distress scores also favored ORM-12741 (p=0.034). The NPI caregiver distress score decreased by a mean (SD) of 22.4 (4.8) points in the low-dose group and by 22.1 (3.4) points in the high-dose group, while no change was observed (mean 0.4, SD 4.9) in the placebo group.

Caveats from Alzheimer's trial: It is worth noting here some caveats to these results. No adjustments were made for multiple comparisons, so some of the positive results may have occurred due to chance. In addition to the 3 out of 4 CDR composite scores that showed no treatment effects, there were numerous other measures (including COWAT, CFT, CSDD, CFQ, CGI-C) that showed negative results. Also, the memory decline observed in the placebo group was relatively large, which may have made the proposed treatment effects more pronounced. More clarity on ORM-12741 treatment effects will be gained when the larger Alzheimer's trial results are published. This phase 2 study called Nebula was initiated in June 2015, and compared a 12-week course of ORM-12741 (low-dose or high-dose, twice daily vs placebo) in 300 people with Alzheimer's and clinically significant agitation and aggression (NCT02471196; Porsteinsson and Antonsdottir, 2017). Agitation and aggression subscores were the primary outcome measures. This trial was completed in 2018, but its results are not published yet.

Biomarker study: In a small clinical biomarker study of 8 Alzheimer's and 8 age-matched controls, there was a down-regulation of α2C adrenergic receptor gene expression in the lymphocytes of Alzheimer's patients compared to controls (Kalman et al., 2005). It is unknown whether α2C adrenergic receptor gene expression is also downregulated in the brains of Alzheimer's patients.

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

In rodents, ORM-12741 treatment attenuated drug (MK-801, PCP)-induced and age-related memory deficits and showed antidepressant-like effects (decreased immobility in a forced swim test)(reviewed in Uys et al., 2017; original research article or abstract/poster was not accessible on PubMed).

In a rat model of post-traumatic epilepsy (following traumatic brain injury), ORM-12741 had no favorable effects on motor and cognitive outcomes (Nissinen et al., 2017).

Effects in the striatum: Because α2C adrenergic receptors are highly expressed in the striatum, they appear to modulate striatal (but not hippocampal) release of dopamine, serotonin, and GABA release (Uys et al., 2017). Combining haloperidol with the selective α2C adrenergic receptor antagonist ORM-10921 increased striatal neurotrophic BDNF levels in these animals, while at the same time improving cognitive deficits, though α2C antagonism alone did not have this benefit, and it is not known whether ORM-12741 also has these properties.

APOE4 interactions: Unknown.

Aging and related health concerns: No studies, clinical or preclinical, have evaluated the efficacy of ORM-12741 on age-related health conditions. ORM-12741 failed to improve symptoms in people with systemic sclerosis in a small phase 2a trial.

Types of evidence:

- None available

No studies have evaluated the efficacy of ORM-12741 on age-related conditions.

ORM-12741 was originally under development for the treatment of Reynaud's phenomenon, a condition in which extremities (fingers/toes) become numb or cold in response to cold temperatures or stress. However, a small phase 2a double-blind randomized placebo-controlled trial that enrolled 12 patients with systemic sclerosis (who have Reynaud's phenomenon) failed to show expedited recovery from a cold challenge with ORM-12741 (single dose of 30 mg or 100 mg), and in fact ORM-12741 prolonged, rather than attenuated, cold-induced vasoconstriction and delayed reperfusion (Herrick et al., 2014).

Altered adrenergic function is thought to contribute to the pathogenesis of Raynaud's phenomenon, and α2C-adrenoceptor likely plays a key role in mediating cold-induced vasospasm (Herrick et al., 2014). However, based on the negative/contrary results, the authors speculated that ORM-12741 increases sympathetic tone by blocking α2C-adrenoceptors in the central nervous system, which in turn may cause release of noradrenaline at sympathetic nerve endings that acts on α1-adrenoceptors to induce vasoconstriction.

Safety: ORM-12741 has been well-tolerated in multiple phase 1 and 2 studies, though it is not clear how the drug affects organs (e.g., kidney, uterus, prostate) that express α2C-adrenoceptors at much higher levels compared to the brain.

Types of evidence:

- 2 clinical trials, 1 in Alzheimer's and 1 in systemic sclerosis

Alzheimer's trial: In a phase 2 double-blind randomized placebo-controlled trial that enrolled 100 Alzheimer's patients with neuropsychiatric symptoms, ORM-12741 treatment (30-60 mg or 100-200 mg, daily) was well-tolerated for most patients (Rinne et al., 2016). Study treatment dosage was reduced for 8 subjects (8%): 2 subjects receiving low-dose ORM-12741 (60–30 mg), 3 subjects receiving high-dose ORM-12741 (200–100 mg), and 3 subjects receiving placebo (reduced to half). There were no notable differences in the frequency of adverse events among the two treatment and one placebo groups. One subject experienced cholestasis with asymptomatic high liver enzyme values after 4 weeks of high-dose treatment. This was reported as a serious adverse event and the subject discontinued the trial. There were no clinically meaningful changes from baseline in the mean safety laboratory values. Standing heart rate values in the high-dose group were slightly above those in the placebo group. However, no statistically significant treatment effect was observed, and no clinically meaningful changes were seen in blood pressure and 12-lead ECG variables, including the QTc interval.

ORM-12741 had previously demonstrated concentration-dependent α2C-adrenoceptor occupancy *in vivo* in the human brain measured with PET imaging (Lovro et al., unpublished results; NCT00829907; discussed in Rinne et al., 2016).

Systemic sclerosis trial: A small phase 2a double-blind randomized placebo-controlled trial that enrolled 12 patients with systemic sclerosis tested acute effects of ORM-12741 (single dose of 30 or 100 mg, or placebo, in a crossover protocol) and found that ORM-12741 was well-tolerated (Herrick et al., 2014). A total of 26 adverse effects were reported in 10 subjects after commencement of study treatment, but there were no serious adverse effects. Headache was the most common adverse effect, with 8 events (3 placebo, 5 active treatment) in 4 patients. There were no statistically significant changes in heart rate or systolic or diastolic blood pressure during the treatment periods. There were no clinically significant changes in ECG.

General concerns: It is worth noting that α2C-adrenoceptors are prominently expressed outside of the brain, including the kidney, spleen, prostate, uterus, and endometrium (Human Protein Atlas).

Expression levels are highest in the cervix/uterine, approximately 4-fold that of expression in the caudate nucleus. It is not clear what effects ORM-12741 may have on these peripheral organs.

Drug interactions: Unknown.

Sources and dosing: ORM-12741 was being developed for Alzheimer's disease by Orion Corporation, but Denovo Biopharma LLC licensed it in June 2019, gaining global rights to develop, manufacture, and commercialize ORM-12741 (PR Newswire). The phase 2a trial in Alzheimer's tested two dose ranges: 30-60 mg/day and 100-200 mg/day (Rinne et al., 2016). Subjects in both treatment arms improved on episodic memory scores, but not on other cognitive scores.

Research underway: No clinical trials are currently ongoing with ORM-12741. There have been 12 completed and 1 terminated trial, according to ClinicalTrials.gov. The larger phase 2 trial in 308 Alzheimer's patients was completed in 2018, but its results are not published (NCT02471196).

Although there has been recent development in PET radiolabeling of α2C-adrenoceptors, ORM-13070 is a substrate for the efflux P-glycoprotein transporter, resulting in very low CNS penetration (Corboz et al., 2011).

Search terms:
Pubmed, Google:

- ORM-12741, DB-105

Websites visited for ORM-12741 and DB-105:

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

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