



*Cognitive Vitality Reports<sup>®</sup> 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.*

## VX-765

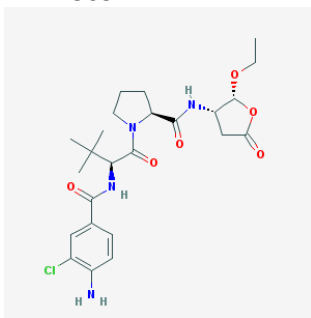
### Evidence Summary

Decreases inflammation in preclinical models of Alzheimer's, arthritis, and acute myocardial infarction. Only 2 small clinical trials have been carried out and 1 subsequent trial was terminated by the sponsor.

**Neuroprotective Benefit:** Mouse studies suggest potential benefit in Alzheimer's and menopause-related cognitive dysfunction, but no evidence for neuroprotection has been demonstrated in humans yet.

**Aging and related health concerns:** Benefits are seen in rodent models of arthritis and ischemia/reperfusion injury (when given prior to injury); no evidence exists for humans yet.

**Safety:** VX-765 has only been tested in 2 small clinical trials; common adverse events included dizziness and headache. A follow-up phase 2b study in partial onset epilepsy patients was terminated by the sponsor.

<b>Availability:</b> under clinical development	<b>Dose:</b> 900 mg TID in a phase 2 trial of patients with treatment-resistant partial epilepsy ( <a href="#">phase 2</a> )	<b>Chemical formula:</b> C <sub>24</sub> H <sub>33</sub> ClN <sub>4</sub> O <sub>6</sub> <b>MW:</b> 509
<b>Half life:</b> not available	<b>BBB:</b> The metabolite, VRT-043198, is BBB-penetrant.	 <p>Source: <a href="#">PubChem</a></p>
<b>Clinical trials:</b> Only 2 clinical trials have been completed, of which the larger one included 64 participants with psoriasis ( <a href="#">phase 2</a> ) and the other trial included 60 patients with partial epilepsy ( <a href="#">phase 2</a> ).	<b>Observational studies:</b> none	

**What is it?** VX-765 (Belnacasan) is a selective IL-1 $\beta$  converting enzyme (ICE)/caspase-1 inhibitor developed by Vertex Pharmaceuticals. VX-765 is a prodrug that is rapidly metabolized to VRT-043198, which is bioavailable and blood-brain barrier permeable ([Boxer et al., 2010](#)). VX-765 is under clinical development for the treatment of inflammatory and autoimmune conditions as it inhibits the heightened response to inflammatory stimuli ([DrugBank](#)). Two phase 2 clinical trials have been completed, one in psoriasis and one in partial epilepsy ([NCT01048255](#); [NCT00205465](#)).

**Neuroprotective Benefit:** Mouse studies suggest potential benefit in Alzheimer's and menopause-related cognitive dysfunction, but no evidence for neuroprotection has been demonstrated in humans yet.

*Types of evidence:*

- 3 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:* None available.



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

In a mouse model of Alzheimer's (J20 mice), VX-765 treatment (10, 25, or 50 mg/kg; 3 times per week for 3 weeks) dose-dependently reversed episodic and spatial memory impairment to scores comparable to wild-type mice treated with vehicle ([Flores et al., 2018](#)). Cessation of VX-765 treatment resulted in the reappearance of memory deficits while resuming treatment re-established normal cognitive functions.

VX-765 treatment also prevented progressive amyloid beta peptide deposition, reversed brain inflammation (decreased Iba1 and GFAP levels in the hippocampus and cortex), and normalized synaptophysin protein levels in the hippocampus. In human neurons, VX-765 protected against stress-mediated neuritic beading (swelling). Interestingly, caspase-1 null J20 mice were protected from episodic and spatial memory deficits, neuroinflammation, and A $\beta$  accumulation, suggesting that caspase-1 inhibition may be beneficial against Alzheimer's-related pathologies and cognitive dysfunctions.

In a mouse model of menopause (ovariectomy), there is increased levels of inflammation (IL-1 $\beta$ , IL-18, NLRP3 expression) and active caspase-1 in the hippocampus ([Xu et al., 2016](#)). Ovariectomy also resulted in an increase in the level of TLR-2 and TLR-4, active NF- $\kappa$ B, pro-IL-1 $\beta$  and pro-IL-18. In these mice, treatment with VX-765 (25 or 50 mg/kg) ameliorated depression- and anxiety-like behavior and reversed the increased levels of IL-1 $\beta$  and IL-18 in the hippocampus.

The primary mechanism of action for neuroprotection is its inhibition of ICE/caspase-1 and caspase-4, which leads to decreased proinflammatory markers including IL-1 $\beta$ , IL-18, IFN- $\gamma$ , IL-4, MCP1, and MIP1- $\alpha$  ([Wannamaker et al., 2007](#)).

*APOE4 interactions:* Unknown.

**Aging and related health concerns:** Benefits are seen in rodent models of arthritis and ischemia/reperfusion injury (when given prior to injury); no evidence exists for humans yet.

*Types of evidence:*

- 1 clinical study testing PBMCs from patients with familial cold autoinflammatory syndrome
- 5 laboratory studies



**Inflammation:** POTENTIAL BENEFIT BASED ON IN VITRO STUDIES. Mutations in the CIAS1 gene (also known as NALP3 and PYPAF1) have been linked to a group of related autoinflammatory syndromes that include familial cold autoinflammatory syndrome ([Aksentijevich et al., 2002](#)). CIAS1 encodes cryopyrin, an adaptor protein expressed in immune cells. Mutations in cryopyrin are hypothesized to result in abnormal secretion of caspase-1-dependent proinflammatory cytokines, IL-1 $\beta$  and IL-18. In a study using peripheral blood mononuclear cells (PBMCs) from familial cold autoinflammatory syndrome patients, LPS induced marked secretion of IL-1 $\beta$  and IL-18 ([Stack et al., 2005](#)). There was no evidence for increased basal secretion of these cytokines. VX-765 treatment dramatically blocked LPS-induced IL-1 $\beta$  and IL-18 secretion in PBMCs from familial cold autoinflammatory syndrome patients as well as from controls. Secretion of IL-6 was not increased in PBMCs from patients compared with control subjects.

**Arthritis:** POTENTIAL BENEFIT IN PRECLINICAL MODELS. In a collagen-induced arthritis model, VX-765 significantly reduced paw inflammation score in a dose-dependent manner, both prophylactically and as a treatment ([Wannamaker et al., 2007](#)). VX-765 at 100 mg/kg dose was as efficacious as prednisolone at 5 mg/kg dose. In a more recent study, of which the full text was unavailable, VX-765 prophylactic treatment (intraperitoneal injection, 100 mg/kg, twice daily) significantly reduced joint clinical scores, suppressed bone marrow edema and synovitis, prevented bone erosion, and decreased histologic scores and serum cytokine levels ([Zhang and Zheng, 2016](#)).

**Ischemia:** POTENTIAL BENEFIT IN PRECLINICAL MODELS. In a rat model of acute myocardial infarction (ischemia-reperfusion injury), administration of VX-765 (i.v. bolus of 32 mg/kg) before reperfusion significantly decreased infarct size to  $29.2 \pm 4.9\%$  (% of risk zone) compared to over 60% in the control (DMSO) treatment ([Audia et al., 2018](#)). Ticagrelor, a P2Y<sub>12</sub> purinergic receptor antagonist, also decreased infarct size to  $42.8 \pm 3.3\%$ . When VX-765 and ticagrelor were combined, infarct size was further decreased to  $17.5 \pm 2.3\%$ . VX-765 treatment decreased circulating IL-1 $\beta$ , prevented loss of cardiac glycolytic enzymes, preserved mitochondrial complex I activity, and decreased release of lactate dehydrogenase, a marker of pyroptosis (highly inflammatory form of programmed cell death). VX-765 prevented reperfusion injury that occurred during reperfusion rather than during ischemia. A single bolus of VX-765 in combination with cangrelor (approved as an antiplatelet drug and also a P2Y<sub>12</sub> antagonist) resulted in marked preservation of left ventricular function and an infarct size that continued to be small after 3 days post-reperfusion, suggesting long-term preservation of heart muscle. While VX-765 may not be beneficial after ischemia/reperfusion, it may be a suitable agent for use in acute myocardial infarction (AMI) patients undergoing percutaneous coronary intervention (PCI).

Other related studies from the same group showed similar benefit. VX-765 treatment (30 uM given throughout ischemia and reperfusion period) significantly reduced infarct size (28% vs 48% in control) to an extent similar to ischemic preconditioning (30%) ([Do Carmo et al., 2018](#)). In rats undergoing coronary artery occlusion, VX-765 treatment (16 mg/kg, i.v. bolus 30 minutes prior to occlusion) significantly reduced infarct size to 39.6% compared to 73.7% in untreated hearts ([Yang et al., 2017](#)). Combining the P2Y12 antagonist cangrelor (antiplatelet drug and P2Y12 antagonist) and VX-765 was highly protective, resulting in only 14.0%  $\pm$  2.9% infarction. The ability of VX-765 to provide protection beyond that of an antiplatelet alone suggests it may be an attractive candidate therapy in acute myocardial infarction. However, protection was observed when VX-765 was given prior to coronary artery occlusion. This mode of administration is not suitable for treatment of acute myocardial infarction after the onset of myocardial ischemia.

**Safety:** VX-765 has only been tested in 2 small clinical trials; common adverse events included dizziness and headache. A follow-up phase 2b study in partial onset epilepsy patients was terminated by the sponsor.

*Types of evidence:*

- 2 clinical trials, 1 in treatment-resistant partial onset epilepsy and 1 in psoriasis

Only 2 clinical trials have been carried out, and neither of the studies' results have been published in peer-reviewed journals. Based on a press release by Vertex, the safety profile for VX-765 was similar to that for placebo in a double-blind randomized placebo-controlled trial of 60 patients with treatment-resistant partial onset epilepsy ([investors.vrtx.com](http://investors.vrtx.com)). The most common adverse events observed across both treatment groups were headache, dizziness, fatigue, and gastrointestinal disorders, and most of these adverse events were mild to moderate. The only adverse event that was 10 percent or greater in frequency in the VX-765 group compared to the placebo group was dizziness. One patient discontinued treatment due to adverse events during the study and was in the VX-765 treatment group.

**Drug interactions:** The clinical trial in patients with treatment-resistant partial-onset epilepsy suggested that VX-765 (or the metabolite VRT-043198) does not interact with commonly administered antiepilepsy drugs ([Chen et al., 2013](#)). Drug interactions with other drugs are unknown.

**Sources and dosing:** VX-765 (Belnacasan) was developed by Vertex Pharmaceuticals. VX-765 is a prodrug that is rapidly metabolized to VRT-043198, which is bioavailable and blood-brain barrier



permeable ([Boxer et al., 2010](#)). A phase 2 trial used a dose of 900 mg three times a day in patients with treatment-resistant partial epilepsy ([NCT01048255](#)).

**Research underway:** There are no ongoing clinical trials testing VX-765 according to [ClinicalTrials.gov](#). There have only been 2 clinical trials, 1 in treatment-resistant partial epilepsy ([NCT01048255](#)) and 1 in psoriasis patients ([NCT00205465](#)). While a follow-up phase 2b study in treatment-resistant partial epilepsy was registered in December 2011, it has since been terminated by the sponsor ([NCT01501383](#)). Based on DrugBank, VX-765 is under clinical development for the treatment of inflammatory and autoimmune conditions as it inhibits the heightened response to inflammatory stimuli ([DrugBank](#)). However, no additional trials have been registered on ClinicalTrials.gov.

**Search terms:**

Pubmed, Google: VX-765, VX765, Belnacasen

Websites visited for VX-765:

- [ClinicalTrials.gov](#)
- Examine.com (0)
- Treato.com (0)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com (0)
- WebMD.com (0)
- [PubChem](#)
- [DrugBank.ca](#)
- Labdoor.com (0)
- ConsumerLab.com (0)
- Cafepharm (0)
- Pharmapro.com (0)



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*If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact [INFO@alzdiscovery.org](mailto:INFO@alzdiscovery.org). To view our official ratings, visit [Cognitive Vitality's Rating page](#).*