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.

Azeliragon (also known as TTP488 and PF-04494700)

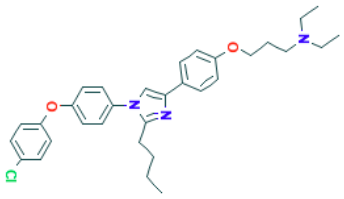
Evidence Summary

Azeliragon is being developed by vTv Therapeutics. It recently failed in a phase 3 clinical trial for Alzheimer's disease.

Neuroprotective Benefit: Potentially beneficial, but narrow therapeutic window. Phase 3 trial in Alzheimer's disease failed.

Aging and related health concerns: RAGE activation may be involved in some aging-related diseases. Azeliragon has not been tried in other indications though.

Safety: Azeliragon is associated with gastrointestinal side effects at low doses. There is a narrow therapeutic window – high dose increases frequency of falls, confusion, and decreases cognition.

Availability: None, Phase 3 planned for 2019	**Dose**: 15mg/day for 6 days then 5mg/day after for Alzheimer's patients	**Chemical formula:** $C_{32}H_{38}ClN_3O_2$ **MW**: 532.125  Source: Pubchem
Half life: Not reported	**BBB**: Yes (but data not published)	
Clinical trials: 1 phase 1 safety study, 1 phase 2 study, 1 phase 3 study	**Observational studies**: None	

What is it?

Azeliragon is an inhibitor of the receptor for advanced glycation endproduct (RAGE). RAGE is expressed on multiple cell types including, neurons, microglia, endothelial cells, macrophages, cardiomyocytes, podocytes, epithelial cells, and smooth muscle cells. It binds to numerous ligands including HMGB1 (amphoterin), S100B, integrin Mac-1, phosphatidylserine, and beta-amyloid. RAGE is a pattern recognition receptor, meaning that it binds to particular protein conformations rather than sequences. Ligand binding to RAGE is implicated in many chronic conditions including chronic inflammation, atherosclerosis, diabetes, and Alzheimer's disease.

RAGE's role in Alzheimer's disease is thought to be two-fold: it may bind to beta-amyloid in the plasma and mediate its influx into the brain, and beta-amyloid may bind to RAGE on neurons or microglia and mediate intraneuronal beta-amyloid transport, increase in oxidative stress, and exacerbate neuroinflammation (Cai et al, 2016; Walker et al, 2015).

In vitro studies suggest that azeliragon prevents the binding of many ligands to RAGE. In theory, the potential pleiotropic effects of azeliragon (e.g. preventing influx of beta-amyloid, reducing neuroinflammation, etc.) make it a promising target for Alzheimer's disease. However, a phase 2 study was stopped early for futility. In a follow-up for cognitive outcomes, investigators reported benefits with a low-dose, especially in individuals with the lowest 40% of plasma concentration of the drug. A phase 3 trial of azeliragon failed in April 2018.

Neuroprotective Benefit: *Potentially beneficial, but a narrow therapeutic window. Phase 3 trial in Alzheimer's disease failed.*

Types of evidence:

- *0 meta-analyses or systematic reviews*
- *1 phase 1 safety study, 1 phase 2 efficacy study, 1 phase 3 efficacy study*
- *1 preclinical study with a related drug*
- *Multiple biomarker studies on the target*

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

None

Human research to suggest benefits to patients with dementia.

Histopathology and biomarkers

Biomarker studies suggest that RAGE levels may be associated with dementia severity. Wilson et al (2009) found that blood RAGE autoantibody levels correlated with Alzheimer's severity, and particularly in the cognitive domains of language and memory. RAGE expression was increased in areas associated with Alzheimer's pathology (e.g. hippocampus), on microglia, and in cerebral blood vessels in post-mortem Alzheimer's brain tissue compared to non-demented controls. Increased expression correlated with disease severity (Lue et al, 2009; Lue et al, 2001).

The transmembrane form of RAGE mediates its cellular effects. Soluble RAGE (sRAGE) is an alternatively spliced form of RAGE that lacks the transmembrane domain, circulates through the blood, and does not mediate downstream cellular effects. sRAGE is thought to be protective by binding to beta-amyloid and AGEs, thereby preventing binding to the RAGE receptor. sRAGE was decreased in patients with MCI, Alzheimer's, and vascular dementia. The lowest levels of sRAGE (<225pg/ml) anticipated a faster time to death (Ghidoni et al, 2008). Although the results have not been replicated, the variability between subjects, and the inability to differentiate between types of dementia or chronic disease, makes it unlikely to be a valuable diagnostic tool (Xu et al, 2016).

Clinical Trials

A phase 1, 10-week safety study in 67 patients found that azeliragon was safe with no serious adverse events (SAEs). There were no changes in plasma inflammatory biomarkers (Sabbagh et al, 2011).

A phase 2 study in 399 patients with mild-to-moderate Alzheimer's was planned to last 18 months using a high dose (60mg/day for 6 days followed by 20mg/day after), a low dose (15mg/day for 6 days and 5mg/day after), and placebo. In a 6-month interim analysis, it was discovered that the high dose group had increased number of falls and confusion and greater decline on ADAS-cog (which was reversible). Therefore, the high dose study was discontinued. 12 months after the last subject was dosed, a data safety monitoring board recommended that the trial be stopped for futility. Patients were taken off the drug, but were offered the opportunity to be followed for the duration of the trial (Galasko et al, 2014).

Of the 132 patients enrolled in the low-dose group, only 11 completed treatment for the entire 18 months while 69 completed a cognitive assessment at 18 months (Walker et al, 2015). The low-dose group was statistically significantly less impaired than placebo on the ADAS-cog (by 3.1 points), with no significant differences in CDR-SB, ADCS-ADL, or NPI scores. There were no differences in hippocampal volume measures or CSF biomarker measures (Galasko et al, 2014).

A follow-up analysis showed that patients with mild Alzheimer's were statistically significantly less impaired with ADAS-cog scores than placebo with favorable trends on CDR-SB and ADCS-ADL. Separating groups by plasma levels of azeliragon, those in the lowest 40% (0.1-16.8 ng/ml) showed greater improvement in ADAS-cog scores, those in the middle 20% (17.0-46.3 ng/ml) had scores similar to placebo, and those in the highest 40% (46.8-167.0) showed clinical worsening compared to placebo (they did not analyze CDR-SB or ADCS-ADL) (Burnstein et al, 2014).

This suggests that there is a narrow therapeutic window and narrow patient population within which azeliragon may be beneficial. Indeed, the phase 3 study in Alzheimer's patients failed in early 2018. However, in a post-hoc analysis, it was reported that azeliragon improved cognition in a subset of patients with diabetes. However, the number of patients with diabetes was very small and this will have to be confirmed in a larger study.

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

Preclinical studies with azeliragon have not been published, but the manufacturer reported that it improved cognition and reduced plaque formation in Alzheimer's transgenic models. Another RAGE inhibitor, FPS-ZM1, reduced RAGE-mediated influx of circulating beta-amyloid into the brain, inhibited beta secretase activity, reduced beta-amyloid production, reduced amyloid plaque formation, improved cerebral blood flow, improved cognition, and suppressed inflammation (Deane et al, 2012).

RAGE is expressed on microglia, neurons, and epithelial cells in the brain. Its expression is generally low in healthy animals. Overexpression studies have been used to tease apart what cells types might contribute to Alzheimer's pathology.

Arancio et al (2004) created a transgenic mouse model that overexpressed APP and RAGE in neurons and reported increased microgliosis and astrocytosis, cognitive deficits, synaptic deficits, and a decrease in acetylcholine neurites in the hippocampus compared to APP single and RAGE single transgenic models. When APP/RAGE mice were crossed with mice expressing dominant-negative RAGE in neurons, the pathologies and deficits were reduced. Similarly, Fang et al (2010) created a transgenic mouse model that overexpressed APP in neurons and RAGE in microglia. They reported many of the same pathologies including increased expression of IL-1β and TNFα, increased microgliosis and astrocytosis, cognitive deficits, an increase in amyloid plaque load, and a decrease in acetylcholine neurites. Again, these pathologies and deficits were reduced when a RAGE receptor with impaired signal transduction was expressed.

On the other hand, Vodopivec et al (2009) reported that a RAGE -/- Alzheimer's transgenic model had decreased levels of insoluble beta-amyloid and increased levels of insulin degrading enzyme earlier in life than an Alzheimer's transgenic control, but in old age there were no differences in plaque accumulation, cognition, or microgliosis.

The reasons for these mixed results between the genetic models and drug studies are not clear.

APOE4 interactions: Not reported in clinical trials.

Aging and related health concerns: *RAGE activation may be involved in some aging-related diseases. Azeliragon has not been tried in other indications though.*

Types of evidence:

- *0 meta-analyses or systematic reviews*
- *0 clinical trials and 0 observational studies*
- *0 preclinical studies on drug intervention*
- *Some biomarker studies*

Cardiovascular disease and diabetes

Some studies suggest an association with RAGE and atherosclerosis in diabetic patients. Expression of RAGE in atherosclerotic plaques in diabetics was greater than in non-diabetics (Burke et al, 2004). Additionally, non-diabetic young subjects with angiographically proven coronary artery disease (CAD) have increased mRNA expression of RAGE in peripheral blood mononuclear cells compared to healthy control, and this expression correlated with levels of hsCRP (Mahajan and Dhawan, 2013).

As in Alzheimer's disease, the protective form of RAGE, sRAGE, is inversely associated with cardiovascular disease. In non-diabetic men, lower plasma levels of sRAGE were associated with the presence of coronary artery disease (CAD) (Falcone et al, 2005). Additionally, in non-diabetic patients with suspected CAD, low sRAGE levels were predictive of low flow-mediated dilation and of increased risk for a major adverse cardiovascular event 48 months later (Chiang et al, 2009).

In ApoE-/- animal models, RAGE knockout attenuates plaque size and reduces the expression of adhesion molecules and RAGE ligands in plaques (Soro-Paavonen et al, 2008; Mahajan and Dhawan, 2013).

Safety: *Azeliragon is associated with gastrointestinal side effects at low doses. There is a narrow therapeutic window – high dose increases frequency of falls, confusion, and decreases cognition.*

Types of evidence:

- *0 meta-analyses or systematic reviews*
- *1 phase 1 safety study and 1 phase 2 efficacy study*

A phase 2 efficacy study in 399 patients with mild-to-moderate dementia was conducted for 18 months. The high dose (60mg/day for 6 days followed by 20mg/day thereafter) was stopped after 6 months because of an increased number of falls and confusion in patients as well as a decline in cognition. In the low-dose group, there were increased gastrointestinal side effects (diarrhea, constipation, and nausea) but a decrease in psychiatric disorders.

Drug interactions:

No information yet because it is not on the market nor are any RAGE inhibitors. In the current clinical trial, there are no specific medicines listed as exclusion criteria except for prescription medical foods intended for the dietary management of the metabolic processes associated with Alzheimer's disease.

Sources and dosing:
Azeliragon is not currently available.

Research underway:
There are no current clinical trials ongoing for azeliragon. However, a clinical trial in type 2 diabetic patients with mild Alzheimer's disease is planned for 2019.

Search terms (not a complete list):
Pubmed:
azeliragon, PF-04494700, TTP488
RAGE + Alzheimer's, atherosclerosis, aging, longevity