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.

Troriluzole (also known as Trigriluzole, BHV-4157, and FC-4157)

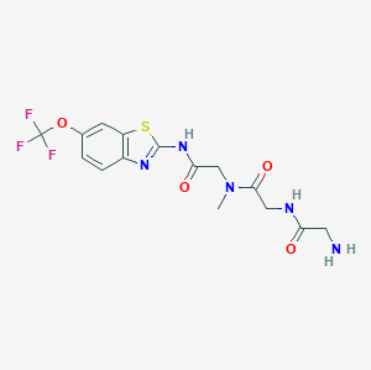
Evidence Summary

As a prodrug of riluzole, troriluzole may have better bioavailability and lower liver burden. However, the phase 2/3 trial for Alzheimer's failed to improve cognitive function and disease severity.

Neuroprotective Benefit: The phase 2/3 trial for Alzheimer's disease failed to improve primary endpoints of cognitive and functional outcomes. Preclinical studies of riluzole suggest neuroprotective benefit, though troriluzole is a substrate of P-glycoprotein.

Aging and related health concerns: No studies with troriluzole have been carried out for age-related diseases.

Safety: Several phase 2/3 clinical trials have reported that troriluzole is well-tolerated. However, no peer-reviewed articles have been published with troriluzole data and details of the types and incidences of adverse events are unknown.

Availability: In clinical trials.	**Dose**: Dose has not been established. The phase 2/3 randomized controlled trial in mild to moderate Alzheimer's disease tested a dose of 280 mg orally once daily.	**Chemical formula:** $C_{15}H_{16}F_3N_5O_4S$ **MW**: 419.4  Source: PubChem
Other names: Trigriluzole, BHV-4157, and FC-4157		
Half life: Not documented.	**BBB**: Not documented but riluzole is penetrant.	
Clinical trials: A phase 2/3 trial in Alzheimer's patients included 350 participants.	**Observational studies**: None.	

What is it? Troriluzole is a tripeptide prodrug formulation of riluzole, a medication used to treat amyotrophic lateral sclerosis (Alzforum). Troriluzole is taken orally and aminopeptidases in the blood release riluzole from a tripeptide carrier. Troriluzole is actively absorbed in the gut via the peptide transporter PepT1, is not subject to a negative food effect, bypasses first-pass metabolism, reduces riluzole burden on the liver, and can be administered once daily (Biohaven website). In contrast, riluzole requires twice daily dosing, has lower bioavailability, and requires fasting for 6 hours/day (cannot be taken with meals). Troriluzole is under clinical development by Biohaven Pharmaceuticals for indications including Alzheimer's disease and spinocerebellar ataxia (Biohaven website). The Alzheimer's trial, which was a phase 2/3 double-blind randomized controlled trial, has failed to show significant effects in the co-primary outcomes of ADAS-Cog11 and CDR-Sum of boxes (NCT03605667; Biohaven press release, 1/18/2021). However, additional analyses of secondary and exploratory efficacy endpoints and biomarker data are still pending and expected to be released soon. Troriluzole is also being tested in people with obsessive compulsive disorder.

Riluzole decreases presynaptic glutamate release (Martin et al., 1993), facilitates glutamate reuptake by astrocytes (Frizzo et al., 2004), acts as a sodium channel blocker, and increases oxidative metabolism with mitochondria-enhancing properties (Mu X et al., 2000).

Neuroprotective Benefit: The phase 2/3 trial for Alzheimer's disease failed to improve primary endpoints of cognitive and functional outcomes. Preclinical studies of riluzole suggest neuroprotective benefit, though troriluzole is a substrate of P-glycoprotein.

Types of evidence:

- 1 phase 2/3 clinical trial in Alzheimer's patients
- 0 observational studies
- 0 laboratory studies
- Several laboratory studies with riluzole

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:
A phase 2/3 double-blind randomized controlled trial evaluated the safety and efficacy of troriluzole in 336 patients with mild to moderate Alzheimer's disease (NCT03605667). Titrated dose of troriluzole to 280 mg orally once daily (starting dose of 140 mg), or placebo, was given for 48 weeks. In December 2019, Biohaven Pharmaceutical announced that this trial advanced past the interim futility analysis (Press release 12/6/2019). The independent Data Safety Monitoring Board communicated that futility was not met based on pre-specified criteria for the interim analysis, which evaluated standard cognitive assessments and hippocampal volume on MRI.

However, in January 2021, Biohaven announced that the phase 2/3 double-blind randomized controlled trial failed to show significant effects of troriluzole in the co-primary outcomes of ADAS-Cog11 and CDR-SB after 48 weeks of treatment compared to placebo (Biohaven press release, 1/18/2021). Troriluzole also failed to differentiate from placebo on the key secondary measure of hippocampal volume assessed by MRI. But a subgroup analysis consisting only of mild Alzheimer's patients showed that troriluzole exhibited a nonsignificant numerical difference of a potential benefit at week 48 on both the ADAS-cog and hippocampal volumetric MRI (-1.1% for troriluzole versus -1.6% for placebo; difference=-0.5%, p=0.2).

Additional analyses of secondary and exploratory efficacy endpoints and biomarker data (e.g., neurofilament light chain, neurogranin, tau, and amyloid) are still pending and expected to be released soon at an upcoming scientific meeting (Biohaven press release, 1/18/2021).

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

Generalized anxiety disorder: NO BENEFIT.
The phase 3 clinical trial testing troriluzole for generalized anxiety disorder has failed (Biohaven press release, 2/10/2020). This was an 8-week trial that randomized 402 adult patients with generalized anxiety disorder. Troriluzole monotherapy at 100 mg twice daily did not differentiate the treatment group from the placebo group on the primary endpoint of the mean change from baseline on an anxiety rating scale (Hamilton Anxiety Rating Scale) after 8 weeks of treatment (-9.28 points with troriluzole vs -9.35 points with riluzole; p=0.917).

Obsessive compulsive disorder (OCD): UNKNOWN. PHASE 3 TRIALS ONGOING.
In a phase 2/3 study of troriluzole treatment (200 mg, once daily) as an adjunctive therapy in OCD patients, there was numerical improvement over placebo on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) at all study timepoints (weeks 4-12) but failed to meet the primary outcome measure at week 12 (p=0.22), however p-value was below 0.05 at week 8 (Biohaven press release 6/24/2020).

Troriluzole treated subjects had a mean Y-BOCS improvement of -5.1 points from baseline versus -3.6 for placebo-treated subjects (difference -1.5; p=0.041; 95% CI: -3.02 to -0.06) at week 8, and -5.9 points in the troriluzole group versus -4.9 points for the placebo group at week 12 (difference -1.0; p=0.220; 95% CI: -2.59 to 0.60).

Differences between troriluzole treatment and placebo were greater in patients who were more severely ill at baseline (Y-BOCS total scores greater than the median score of 26). Troriluzole treated subjects had a mean Y-BOCS change from baseline of -6.0 points versus -3.1 for placebo subjects (difference -2.9; p=0.035; 95% CI: -5.49 to -0.21) at week 8, and -7.0 points in troriluzole subjects versus -4.6 in placebo subjects (treatment difference -2.4; p=0.084; 95% CI: -5.18 to 0.33) at week 12.

In January 2021, Biohaven announced that they commenced enrollment in the pivotal phase 3 trial of troriluzole in OCD (Biohaven press release, 1/4/2021). They are including an increased sample size to adequately power for previously observed treatment effect and a higher dose of troriluzole (280 mg, once daily). Biohaven is running 2 double-blind, placebo-controlled phase 3 clinical trials with identical study designs; they plan to enroll approximately 600 patients in each of these adjunctive treatment trials across study sites in both the US and Europe.

Spinocerebellar ataxia: NO BENEFIT AT 8 WEEKS, BUT BENEFT AT 48 WEEKS; EXTENSION STUDY ONGOING.

There is an ongoing clinical trial testing troriluzole in a phase 2b/3 long-term extension study in spinocerebellar ataxia (Beiner et al., 2019). Spinocerebellar ataxia is a type of hereditary ataxia characterized by degeneration in the cerebellum and sometimes also the spinal cord. Biohaven previously reported negative topline data from this trial at the end of the 8-week randomization phase, such that troriluzole did not differentiate from placebo on the primary endpoint or key secondary outcome measure (Biohaven website). In 2019, based on a poster presented at AAN, troriluzole treatment for 48 weeks during the extension phase was associated with an improvement in disease status with a change in an ataxia score (measured by Scale for the Assessment and Rating of Ataxia, or SARA) of -0.34 points (95% confidence interval [CI], -0.94 to 0.26) after 1 year (Link to poster). This trial was not a placebo-controlled trial, and therefore the comparator was a natural history cohort of patients, which showed a change in SARA score of +1.07 points (95% CI, 0.56 to 1.58) after 1 year (indicating worsening disease status). There was a significant difference between the troriluzole treated group and the natural history cohort of -1.41 points (95% CI, -2.22 to -0.60), suggesting therapeutic benefits with troriluzole (p=0.0007). This trial is still ongoing as the extension phase is a total of 96 weeks.

Riluzole studies: Many more studies have evaluated the effects of riluzole for neuroprotection. For example, studies have reported that riluzole improves cognitive functions in aged rats (Pereira et al., 2014; Pereira et al., 2017), mouse models of Alzheimer's disease (Hunsberger et al., 2015; Mokhtari et al., 2017), and a rat model of brain injury (McIntosh et al., 1996). Some mechanisms of action observed in rodent models included decreased glutamate release (Hunsberger et al., 2015), increased vesicular glutamate transporter 1 levels (which packages glutamate into vesicles), increased glutamate transporter 1 levels (which removes glutamate from extracellular space), reduced oxidative stress markers (Mokhtari et al., 2017), attenuated acetylcholinesterase activity (Mokhtari et al., 2017), decreased tau pathology (Hunsberger et al., 2015), increased clustering of dendritic spines (thought to enhance synaptic strength; Pereira et al., 2014), and increased levels of the brain-derived neurotrophic factor (BDNF) in the hippocampus, which was associated with increased proliferation of precursor cells (Katoh-Semba et al., 2002).

In young and aged rats, many of the gene changes seen in Alzheimer's disease are reversed by riluzole (Pereira et al., 2017). For example, riluzole treatment resulted in an increase in the glutamate transporter (EAAT2) expression in the hippocampus, which suggests that the efficient removal of glutamate may prevent excitotoxicity and underlie neuroprotection and improved cognitive functions.

Animals treated with riluzole had 908 gene transcripts increased and 927 gene transcripts decreased. Notably, there is a large overlap of genes (435) that were changed with aging and were also altered by riluzole treatment. Many pathways reversed by riluzole treatment were related to synaptic transmission and plasticity.

Troriluzole at the blood-brain barrier: Riluzole is a substrate of P-glycoprotein, a transporter highly expressed at the blood-brain-barrier that regulates removal of various molecules from the brain, including cholesterol, lipids, peptides, and brain-active drugs (Milane et al., 2007). Thus, it is likely that troriluzole has the same fate. In ALS, P-glycoprotein expression and activity are increased, resulting in resistance to drugs such as troriluzole/riluzole (Mohamed et al., 2017). In normal aging and in Alzheimer's disease, P-glycoprotein expression appears to be decreased (Chiu et al., 2015), suggesting that resistance to troriluzole/riluzole may be less pronounced; however, as long as P-glycoprotein is present, riluzole is actively pumped out of the brain.

APOE4 interactions: Unknown.

Aging and related health concerns: No studies with troriluzole have been carried out for age-related diseases.

Types of evidence:

- 0 clinical trials
- 0 laboratory studies

Safety: Several phase 2/3 clinical trials have reported that troriluzole is well-tolerated. However, no peer-reviewed articles have been published with troriluzole data and details of the types and incidences of adverse events are unknown.

Types of evidence:

- 1 phase 3 trial in generalized anxiety disorder
- 1 phase 2/3 trial in Alzheimer's patients
- 3 phase 1 clinical trials of troriluzole (unpublished)
- 7 clinical trials of riluzole (4 in ALS, 1 in Huntington's disease, 1 in major depressive disorder, 1 in schizophrenia)

Troriluzole: No clinical studies on troriluzole have been published in peer-reviewed articles. In a phase 3 trial of 402 patients with generalized anxiety disorder, treatment with troriluzole (100 mg twice daily) for 8 weeks was well-tolerated with a low discontinuation rate due to adverse events (troriluzole 4% versus placebo 4.5%)(Biohaven press release). There have also been 3 completed phase 1 clinical trials and troriluzole has been "observed to be well tolerated with no clinically relevant safety signals identified in the completed and ongoing clinical studies" (Biohaven website).

In a phase 2/3 trial testing a titrated dose of troriluzole (280 mg orally once daily, with starting dose of 140 mg/day) for 48 weeks was "relatively well tolerated and demonstrated a safety profile consistent with previous studies of troriluzole" (Biohaven press release, 1/18/2021). No details of the types of adverse events or their incidences were discussed in the press release.

Riluzole: There are many published reports from clinical trials testing riluzole. A Cochrane meta-analysis of 4 randomized controlled trials totaling 1,477 patients with ALS reported that riluzole (100 mg/day) is reasonably safe and likely prolongs median survival by about 2 to 3 months (Miller et al., 2012). However, more treated participants developed a threefold or greater elevation of serum alanine transferase (ALT; measure of liver injury) compared to controls in Lacomblez et al., 1996, Bensimon et al., 2002 and in the combined data (RR=2.62; 95% CI, 1.59-4.31). Nausea was more frequent in riluzole-treated subjects with RR of 1.5 (95% CI, 1.06-2.28). There was a trend toward more asthenia (physical weakness) among the treated participants in each trial, and this became statistically significant when the data from 3 trials were combined (RR=1.50; 95% CI, 1.07-2.12). Five riluzole-treated participants reported circumoral paresthesias (unusual or abnormal sensations around the mouth) in one of the trials (Lacomblez et al., 1996) but this symptom was not reported by any controls (MD=7.71; 95% CI, 1.33-44.84).

A double-blind randomized controlled trial of 63 Huntington's disease patients reported that riluzole treatment (100 or 200 mg/day) for 8 weeks was associated with an elevation in ALT in a dose-dependent manner, though levels normalized within 12 days of drug discontinuation (Huntington Study Group, 2003). One serious adverse event was observed, which was a psychiatric hospitalization in a subject who had received riluzole 200 mg/day, occurring only after riluzole had already been suspended because of other symptoms (fatigue, urinary incontinence, and diaphoresis) that had subsequently resolved. The proportion of subjects reporting adverse events was higher in those receiving riluzole.

Other randomized clinical trials of riluzole, one in major depressive order and the other in schizophrenia, reported no significant differences in adverse events between the riluzole and placebo groups (Salardini

et al., 2016; Farokhnia et al., 2014). Adverse events which occurred at equivalent rates in both riluzole and placebo groups included drowsiness, constipation, dizziness, abdominal pain, increased appetite, decreased appetite, nausea, headache, dry mouth, cough, and diarrhea.

Drug interactions: Drug interactions for troriluzole has not been well-studied but are likely to be similar to those of riluzole. Based on drugs.com, there are 4 major drug interactions and 23 moderate interactions with riluzole. The 4 drugs that can cause major drug interactions with riluzole are leflunomide, lomitapide, mipomersen, and teriflunomide; all of these drugs may cause liver problems and therefore using these with troriluzole/riluzole may increase that risk. Troriluzole/riluzole may also interact with drugs that affect liver enzymes (e.g., caffeine, amitriptyline, omeprazole, rifampin, quinolone antibiotics).

Sources and dosing: Troriluzole is under clinical development by Biohaven Pharmaceuticals for indications including Alzheimer's disease and spinocerebellar ataxia (Biohaven website). The effective dose has not been established. The phase 2/3 randomized controlled in mild to moderate Alzheimer's disease tested a dose of 280 mg orally once daily (titrated to 280, with initial dose at 140 mg/day) (NCT03605667). The phase 3 randomized controlled trial in spinocerebellar ataxia tested a dose of 140 mg orally, once daily (NCT03701399).

Research underway: There are currently 6 ongoing clinical trials testing troriluzole according to ClinicalTrials.gov (as of 5/21/21). There are 3 trials in people with obsessive-compulsive disorder (NCT04693351; NCT04641143; NCT04708834), 2 trials in people with spinocerebellar ataxia (NCT03701399; NCT02960893), and 1 trial in Alzheimer's disease (NCT03605667). The Alzheimer's trial, which was a phase 2/3 double-blind randomized controlled trial, has failed to show significant effects in the co-primary outcomes of cognitive function (ADAS-Cog11) and disease severity (CDR-SB) (NCT03605667; Biohaven press release, 1/18/2021). However, additional analyses of secondary and exploratory efficacy endpoints and biomarker data (e.g., neurofilament light chain, neurogranin, tau, and amyloid) are still pending and expected to be released soon. Biohaven is planning to amend the ongoing long-term extension study for mild Alzheimer's patients to be able to continue treatment to collect additional clinical and biomarker data (Biohaven press release, 1/18/2021).

IP: Composition of matter patent for troriluzole is active until 2039.

Search terms:
Pubmed, Google: troriluzole, trigriluzole, BHV-4157, and FC-4157

Websites visited for troriluzole and trigriluzole:

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