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)

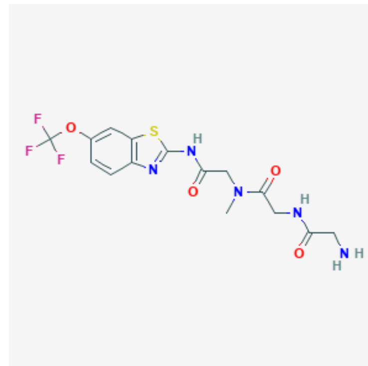
Evidence Summary

As a prodrug of riluzole, troriluzole may have good bioavailability and lower liver burden, but both are P-glycoprotein substrates. Clinical trial results for AD and spinocerebellar ataxia are expected in 2021.

Neuroprotective Benefit: Preclinical and clinical studies of riluzole suggest neuroprotective benefit, though troriluzole is a substrate of P-glycoprotein. Clinical trial results for Alzheimer's and spinocerebellar ataxia are expected in late 2020 or early 2021.

Aging and related health concerns: No studies with troriluzole have been carried out for age-related diseases other than the ones ongoing for neurodiseases (Alzheimer's, spinocerebellar ataxia).

Safety: Several clinical trials have reported it is well-tolerated with up to 8 weeks of treatment, but long-term safety is unknown. Riluzole, the active ingredient, is generally well-tolerated, but nausea and elevated alanine transferase have been reported.

<table>
<tr>
<td>Availability: In clinical trials.</td>
<td rowspan="2">Dose: Dose has not been established. The ongoing phase 2/3 randomized controlled trial in mild to moderate Alzheimer's disease is testing a dose of 280 mg orally once daily. The ongoing phase 3 randomized controlled trial in spinocerebellar ataxia is testing a dose of 140 mg orally once daily.</td>
<td rowspan="4">Chemical formula: $C_{15}H_{16}F_3N_5O_4S$
MW: 419.4

Source: PubChem</td>
</tr>
<tr>
<td>Other names: Trigriluzole, BHV-4157, and FC-4157</td>
</tr>
<tr>
<td>Half life: Not documented.</td>
<td>BBB: Not documented but riluzole is penetrant.</td>
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<tr>
<td>Clinical trials: No trial results have been published in peer-reviewed journal articles. Several trials are ongoing.</td>
<td>Observational studies: None.</td>
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</table>

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).

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: Preclinical and clinical studies of riluzole suggest neuroprotective benefit, though troriluzole is a substrate of P-glycoprotein. Clinical trial results for Alzheimer's and spinocerebellar ataxia are expected in late 2020 or early 2021.

Types of evidence:

- 0 clinical trials (1 ongoing)
- 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:
None currently available, though there is one ongoing phase 2/3 double-blind randomized controlled trial evaluating 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, will be given for 48 weeks. In December 2019, Biohaven Pharmaceutical announced that this trial has advanced past the interim futility analysis (Press release). 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. The interim analysis was designed to allow for stopping the trial early due to futility. To pass the interim futility analysis, troriluzole had to demonstrate numerically greater benefit over placebo on at least one of the two pre-specified criteria at 26 weeks: either cognitive function (as measured by the ADAS-cog) or hippocampal volume (as assessed by MRI). This trial is scheduled to be completed in December 2020.

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). 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).

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 other than the ones ongoing for neurodiseases (Alzheimer's, spinocerebellar ataxia).

Types of evidence:

- 0 clinical trials
- 0 laboratory studies

Safety: Several clinical trials have reported it is well-tolerated with up to 8 weeks of treatment, but long-term safety is unknown. Riluzole, the active ingredient, is generally well-tolerated, but nausea and elevated alanine transferase have been reported.

Types of evidence:

- 1 phase 3 trial in generalized anxiety disorder
- 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).

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 trogriluzole 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 is testing 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 is testing a dose of 140 mg orally once daily (NCT03701399).

Research underway: There are currently 3 ongoing clinical trials testing troriluzole (as of 2/13/2020). One is a phase 2/3 double-blind randomized controlled trial to evaluate 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 (started at 140 mg once daily), or placebo, will be given for 48 weeks. Primary outcome measures are ADAS-Cog11 and CDR-Sum of boxes from baseline to week 48 between the treatment group and the placebo group. In December 2019, Biohaven Pharmaceutical announced that this trial has advanced past the interim futility analysis (Press release). This trial is scheduled to be completed in December 2020. The other ongoing trial is a phase 3 double-blind randomized controlled trial testing troriluzole in 210 adult subjects with spinocerebellar ataxia (NCT03701399). This trial is testing a troriluzole dose of 140 mg/day orally or placebo for 96 weeks (Link to poster). This trial is scheduled to be completed in October 2020. And the third trial, not listed in

ClinicalTrials.gov, is a phase 3 trial testing troriluzole in obsessive compulsive disorder (Biohaven 2020 slide deck). This study is enrolling 226 subjects and are testing the effects of troriluzole (200 mg once daily) versus placebo on an outcome measure called Y-BOCS. The randomization phase is 12 weeks followed by an open-label 48-week extension phase. Topline results are expected in Q2 of 2020.

IP: Composition of matter patent for troriluzole is active until 2036.

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)