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Troriluzole

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Obsessive-compulsive disorder (OCD) is a persistent and often debilitating mental health condition, characterized by intrusive, unwanted thoughts and compulsive behaviours that interfere with everyday life. Impacting 2–3 % of individuals globally, OCD is particularly difficult to manage in patients who exhibit moderate to severe symptoms and have not responded adequately to traditional serotonergic or dopaminergic treatments. Existing therapeutic options, including selective serotonin reuptake inhibitors (SSRIs) and antipsychotic medications, often yield suboptimal results and are associated with undesirable effects such as metabolic disturbances, sexual side effects, and movement disorders. These limitations emphasize the pressing need for innovative drug strategies that address different neurobiological mechanisms [1,2].

One such emerging option is troriluzole, an investigational compound from Biohaven Pharmaceuticals. In contrast to conventional antidepressants, troriluzole targets glutamate regulation—a system increasingly linked to the biological basis of OCD. Research from preclinical models to early clinical studies indicates that excessive glutamatergic activity may be central to the disorder's development. As a prodrug of riluzole, troriluzole is designed to enhance systemic absorption, simplify dosing, and reduce potential liver toxicity. Troriluzole can be actively absorbed in the stomach, eliminating the need for fasting, enabling once-daily dosing, and bypassing first-pass metabolism, thereby reducing burden on the liver. It is hypothesized to modulate glutamate levels by enhancing the expression and function of excitatory amino acid transporters and decreasing presynaptic glutamate release [3].

Troriluzole, a third-generation agent modulating glutamate activity, was shown to help alleviate symptoms of OCD when used alongside existing treatments, particularly in individuals who were either treatment-resistant or presented with severe illness at baseline. A randomized, double-blind, placebo-controlled proof-of-concept trial evaluated 244 adults with Y-BOCS scores of 19 or higher who had not responded adequately to standard therapies. Participants received either troriluzole or placebo for 12 weeks while continuing their usual medications, with evaluations conducted at weeks 4, 8, and 12. Throughout the study, those in the troriluzole group experienced greater numerical improvements in symptom scores than the placebo group, although not all differences reached statistical significance. By week 8, the mean reduction in Y-BOCS score was -5.1 in the troriluzole group compared to -3.6 in the placebo group (-1.5 points; $p = 0.041$). At week 12, the reductions were -5.9 and -4.9, respectively, with a non-significant difference of 1.0 points ($p = 0.22$). Post hoc analyses revealed that patients with more severe symptoms at baseline (Y-BOCS $\geq$ 24) saw even greater benefits, with a week 8 score reduction of 5.7 versus 3.8 ($p = 0.051$) and week 12 reductions of 6.7 versus 5.0 ($p = 0.105$) in the troriluzole and placebo groups, respectively. These findings support the potential of troriluzole to improve outcomes in treatment-resistant OCD [4].

To validate these findings, two Phase 3 multicentre, double-blind, placebo-controlled trials (NCT04641143

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and NCT04693351) were launched. These studies involve adult participants who have been diagnosed with OCD for at least a year and have not experienced sufficient relief from current treatments. Participants needed to score at least 22 on the Y-BOCS to qualify. The main outcome being measured is the change in Y-BOCS scores over a 10-week treatment window. By May 2024, 839 individuals had been enrolled. Analysis of the participant demographics revealed that women made up 65 % of the group, and those aged 18 to 39 years comprised 59 % of all participants. In terms of clinical history, 63 % had been living with OCD for a decade or less, and nearly half (46 %) had a Y-BOCS score of 28 or above, indicating high symptom severity. Most of the study population was drawn from the United States and United Kingdom, accounting for over 86 % of total enrolees. The racial makeup was predominantly White (80.5 %), with Asian (11.4 %) and Black (4.2 %) individuals also represented. Early findings suggest that the troriluzole group experienced statistically significant improvements in OCD symptoms by Week 8, although the difference noted at Week 12, which was the pre-specified primary endpoint, did not achieve statistical significance ($p = 0.22$). Still, the pattern of improvement, particularly among those with more severe symptoms, supports continued research [5,6].

Should troriluzole prove both effective and safe in the final analysis, it would introduce the first novel pharmacological mechanism for OCD in more than 20 years. Its mode of action offers a potentially transformative solution for individuals who have not benefited from existing treatments. Ongoing analysis and future trials are necessary to further assess long-term safety and effectiveness across more diverse populations. However, current data point toward a promising advancement in the pharmacological management of OCD. With its novel target and promising tolerability profile, troriluzole may signal a turning point in how this complex disorder is approached.

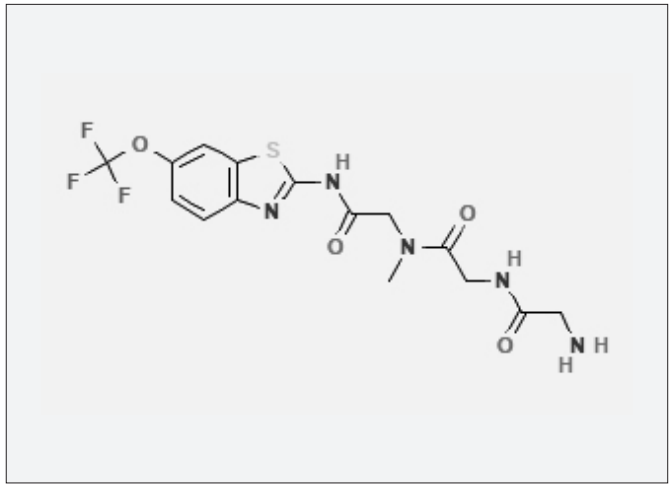

Figure 1. Chemical structure of troriluzole

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