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Troriluzole Exhibits Favorable Hepatic Safety Profile Across a Diverse Range of Disorders

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CONCLUSIONS

1. Riluzole, approved by the US Food and Drug Administration in 1995 for treatment of amyotrophic lateral sclerosis, is a neuroprotective drug that modulates central nervous system glutamatergic neurotransmission, albeit with several limitations, including high first-pass effects in the liver and dose-dependent transaminase elevations.
2. Troriluzole, a novel optimized prodrug of riluzole, was designed to overcome the liabilities of riluzole.
3. This large (N = 1386) database of clinical trial safety data, including data on participants with obsessive compulsive disorder, Alzheimer disease, generalized anxiety disorder, and spinocerebellar ataxia, was used to investigate the hepatic safety profile of troriluzole.
4. Troriluzole exhibited a favorable safety profile, with no reported cases of drug-induced liver injury or Hy's law.
5. The cumulative frequencies of ALT >3 × ULN (2.6%) and >5 × ULN (0.6%) were substantially lower than those reported for riluzole (8% and 2%, respectively), confirming the hepatic safety advantages of troriluzole.

Disclosures: All authors are employed by and hold stock/stock options in Biohaven

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References: 1. Doble A. The pharmacology and mechanism of action of riluzole. *Neurology.* 1996;47(6 Suppl 4):S233-S241. **2.** Silk AW, Saraiya B, Groisberg R, et al. A phase Ib dose-escalation study of troriluzole (BHV-4157), an oral glutamatergic signaling modulator, in combination with nivolumab in patients with advanced solid tumors. *Eur J Med Res.* 2022;27(1):107. **3.** Riluzole. Package insert. sanofi-aventis; 2008. **4.** US Food and Drug Administration. *Guidance Document. Drug-Induced Liver Injury: Premarketing Clinical Evaluation.* 2009. Accessed March 12, 20024. https://www.fda.gov/media/116737/download **5.** Data on file.

Abbreviations: AD, Alzheimer disease; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; BID, twice a day; BMI, body mass index; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; QD, every day; SCA, spinocerebellar ataxia; TBL, total bilirubin; ULN, upper limit of normal.

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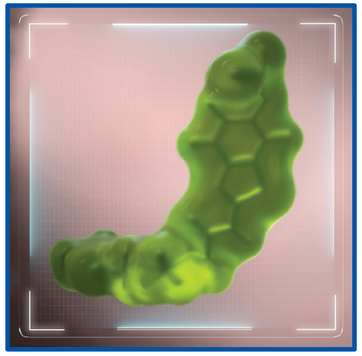
BACKGROUND

- Troriluzole (BHV-4157) is a novel, third-generation, orally administered, tripeptide prodrug of riluzole that is designed to both harness the strengths and overcome the limitations of riluzole.
- FDA-approved nearly 30 years ago for the treatment of amyotrophic lateral sclerosis, riluzole is a neuroprotective drug that modulates central nervous system glutamatergic neurotransmission by blocking neuronal glutamate release and increasing extracellular clearance of glutamate.[1,2]
- Several aspects of riluzole limit its clinical utility, including: very low water solubility; high interindividual pharmacokinetic variability; low bioavailability (~60%); twice-daily dosing and a negative food effect, requiring that riluzole be taken ≥1 hour before or ≥2 hours after any meal; high first-pass effects in the liver; and dose-dependent transaminase elevations.[3]
- Approximately one-half of riluzole-treated patients experienced ≥1 alanine transaminase (ALT) measurement above the upper limit of normal (ULN). At doses of 50 mg twice daily, 8% of individuals taking riluzole experienced ALT elevations >3 × ULN; 2% of individuals experienced ALT >5 × ULN over an 18-month investigation period.[3]
- Troriluzole offers several advantages over riluzole, including: once-daily administration; high oral bioavailability (80-90%) with no negative food effect; and stability in hepatocytes and gastric fluids, allowing for functional bypassing of first-pass metabolism, higher active metabolite concentrations, and reduction of initial hepatic burden (**Figure 1**).
- This analysis assesses the hepatic safety profile of troriluzole in pooled clinical trial data, inclusive of data on participants with obsessive-compulsive disorder (OCD), Alzheimer's disease (AD), generalized anxiety disorder (GAD), or spinocerebellar ataxia (SCA).

Figure 1. Troriluzole Mechanism of Action



OBJECTIVE

- To characterize the hepatic safety profile of troriluzole in pooled clinical trial data across a diverse range of disorders.

METHODS

- Safety data were pooled across 6 phase 2/3 studies (BHV4157-201, BHV4157-202, BHV4157-203, BHV4157-206, BHV4157-207, and BHV4157-209), inclusive of data on individuals who were administered ≥1 dose of troriluzole in either the randomization or open-label extension phase (OLE).
- Troriluzole doses, treatment durations, and study populations differed between phase 2/3 studies. For integration purposes, safety data were pooled by indication and overall for the 6 studies with unblinded and/or open-label data: BHV4157-201 and BHV4157-206 in SCA, BHV4157-202 and BHV4157-209 in OCD, BHV4157-203 in AD, and BHV4157-207 in GAD.
- Study drug exposure summaries included treatment duration, total days on the study drug, average daily dose, and percent adherence. Exposure analyses included data on participants who received ≥1 dose, regardless of differences in duration and dose.
- This analysis reports the number and percentage of participants who experienced on-treatment liver function test (LFT) elevations, including ALT, aspartate transaminase (AST), alkaline phosphatase, or total bilirubin levels, as multiples of ULN.
- Laboratory data were analyzed utilizing test results reported by local laboratories and external central laboratories.
- The summary of participants with on-treatment LFT elevations was presented based on the worst on-treatment laboratory test per the ULN range.
- Prespecified liver-related adverse events (eg, anorexia, fatigue, nausea, vomiting, and abdominal pain) were assessed if they occurred in conjunction with prespecified ALT or AST elevations >3 × ULN.
- A scatter plot (eDISH) was created to depict the maximum ALT ratio of value to ULN against the maximum total bilirubin ratio of value to ULN.

RESULTS

TRORILUZOLE EXPOSURE

- In the 6 phase 2/3 studies, 1386 participants were treated with troriluzole 140 mg, 200 mg, or 280 mg in the randomization or OLE phases. **Figure 2**

Figure 2. Phase 2/3 Studies Included in Hepatic Safety Analysis

- The mean (SD) daily dose of troriluzole across all indications was 204.6 (44.5) mg.
- Mean (SD) treatment duration was 322.5 (343.4) days.
- Participants with SCA experienced a mean (SD) of 621.9 (504.7) days of treatment; those with OCD, AD, or GAD had a mean (SD) duration of 226.0 (198.1), 334.1 (208.1), and 138.4 (91.9) days of treatment, respectively.
- Among participants with SCA, 58 received troriluzole for >3 years, 45 for >4 years, and 32 for >5 years.

DEMOGRAPHICS

- 63.1% of participants were female, and the mean age across all participants at the time of informed consent was 47.8 years. Participants with AD were the oldest population, with a mean age of 71.8 years. **Table 1**
- The mean body mass index across all indications was 27.1 kg/m^2. **Table 1**

Table 1. Participant Demographic Data

	SCA n = 338	AD n = 281	GAD n = 348	OCD n = 419	Total N = 1386
Sex: n (%)					
Female	172 (50.9)	169 (60.1)	268 (77.0)	265 (63.2)	874 (63.1)
Male	166 (49.1)	112 (39.9)	80 (23.0)	154 (36.8)	512 (36.9)
Age at informed consent (years)					
Mean (SD)	49.2 (13.6)	71.8 (8.0)	38.2 (12.8)	38.4 (13.2)	47.8 (17.9)
Age category at informed consent (years): n (%)					
<65	285 (84.3)	57 (20.3)	345 (99.1)	412 (98.3)	1099 (79.3)
≥65	53 (15.7)	224 (79.7)	3 (0.9)	7 (1.7)	287 (20.7)
BMI (kg/m^2) Mean (SD)	26.63 (5.8)	25.77 (4.2)	28.17 (5.7)	27.56 (5.4)	27.12 (5.4)

HEPATIC SAFETY

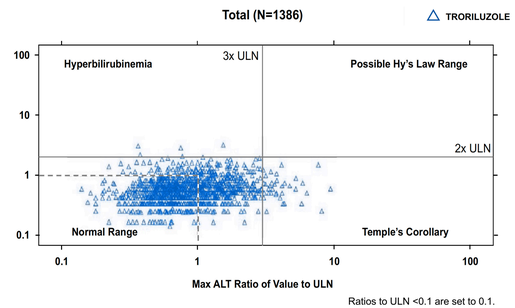
- No participants experienced drug-induced liver injury or Hy's law.[4]
- 40 (3.0%) participants experienced ALT or AST elevations >3 × ULN; 11 (0.8%) experienced ALT or AST elevations >5 × ULN, and 1 (0.1%) participant experienced an AST elevation >10 × ULN (without a similar ALT elevation). **Table 2**
  - There were 35 (2.6%) participants with ALT >3 × ULN and 8 (0.6%) with ALT >5 × ULN.
  - There were 16 (1.2%) participants with AST >3 × ULN and 6 (0.4%) with AST >5 × ULN.
  - No participants experienced ALT or AST elevations >3 × ULN and concurrent liver-related adverse events (anorexia, fatigue, nausea, vomiting, or abdominal pain).

Table 2. Liver Function Test Elevations On Treatment

n (%)	SCA n = 338	AD n = 281	GAD n = 348	OCD n = 419	Total N = 1386
n with liver function test data	337	276	335	397	1345
ALT					
>3 × ULN	6 (1.8)	7 (2.5)	11 (3.3)	11 (2.8)	35 (2.6)
>5 × ULN	3 (0.9)	1 (0.4)	3 (0.9)	1 (0.3)	8 (0.6)
>10 × ULN	0	0	0	0	0
AST					
>3 × ULN	2 (0.6)	3 (1.1)	4 (1.2)	7 (1.8)	16 (1.2)
>5 × ULN	1 (0.3)	0	2 (0.6)	3 (0.8)	6 (0.4)
>10 × ULN	0	0	0	1 (0.3)	1 (0.1)
TBL >2 × ULN	1 (0.3)	2 (0.7)	1 (0.3)	1 (0.3)	5 (0.4)
ALP >2 × ULN	1 (0.3)	0	0	1 (0.3)	2 (0.1)

- 5 (0.4%) participants experienced a total bilirubin >2 × ULN.
  - No participants experienced Hy's law (ALT or AST elevations >3 × ULN in conjunction with total bilirubin >2 × ULN). **Figure 3**
  - On the eDISH scatter plot, data points for nearly all troriluzole-treated participants appeared in the lower left quadrant, indicating LFT values within the range of ALT <3 × ULN and total bilirubin <2 × ULN. (Total bilirubin and ALT values are not necessarily concurrent.)

Figure 3. Evaluation of Drug-Induced Serious Hepatoxicity



Ratios to ULN <0.1 are set to 0.1.