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Safety, Tolerability, and Pharmacokinetics of Single and Multiple Rising Doses of Troriluzole in Healthy Subjects

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CONCLUSIONS

1. Troriluzole was readily absorbed and rapidly converted to its active metabolite riluzole
2. Riluzole was approximately dose proportional across the studied troriluzole dose range
3. Riluzole steady state was achieved by Day 5 following troriluzole once daily dosing at 280 mg, with no clinically meaningful accumulation of riluzole
4. Pharmacokinetics of riluzole administered as troriluzole displays lower variability than generic riluzole and supports once daily dosing
5. Troriluzole was well-tolerated in Phase 1 SAD/MAD studies up to 840 mg and incidence of adverse effects did not increase with dose escalation

Disclosures: HS, BA, KG, EA, DS, IQ, VC, and RB are employed by and hold stock/stock options in Biohaven Pharmaceuticals, Inc.

References: 1. Lacomblez, L. *Neurology*. 1996; 47:s242-250; **2.** Liu J. *Drug Deliv.* 2018. 25(1): 43-48; **3.** Groeneveld GJ. *J Neurol Sci*. 2001. 191(1-2):121-125; **4.** Liboux A. *J Clin Pharmacol*. 1997; 37(9): 820-827; **5.** Bensimon G. *Expert Opin Drug Saf*. 2004. 3(6): 525-534; **6.** Pelletier JC. *ACS Med Chem Lett.* 2018; 9(7): 752-756.

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INTRODUCTION

- Riluzole is a glutamate modulator with neuroprotective effects approved by the Food and Drug Administration (FDA) for the treatment of amyotrophic lateral sclerosis (ALS)[1]
- Riluzole is well-tolerated up to 200 mg in its current formulation and has been previously evaluated in patients with ALS, obsessive-compulsive disorder, and Huntington's Disease[2]
- The current formulation of riluzole limits clinical repurposing due to relatively low oral bioavailability, twice-daily dosing to maintain therapeutic exposures[3], 70% variation in peak serum levels[4], and dose dependent elevation of liver function tests[5]
- Troriluzole is a novel tripeptide prodrug reformulation of riluzole designed to increase absorption and systemic circulation[6]
- Pre-clinical studies revealed optimized features such as enhanced gastrointestinal absorption, minimized first-pass metabolism, and little impact on safety and tolerability
- Troriluzole therapeutic doses range from 200-280 mg as determined in clinical trials

OBJECTIVE

- The objectives of Studies BHV4157-101, BHV4157-103, and BHV4157-108 included the evaluation of the safety, tolerability, pharmacokinetics, and dose proportionality of riluzole, administered orally as troriluzole

METHODS OVERVIEW

- BHV4157-101 was a first-in-human, Phase 1 study in healthy subjects to assess safety, tolerability, and pharmacokinetics of troriluzole doses ranging from 17.5-200 mg as single ascending doses (SAD) in Part 1 and multiple ascending doses (MAD) in Part 2. 58 subjects received drug and 20 received placebo
- BHV4157-103 was a Phase 1 SAD/MAD age-stratified study to assess safety, tolerability, and pharmacokinetics of troriluzole 280 mg doses. Of the 8 subjects receiving troriluzole, 5 were ≥65 years old and 3 were <65 years old. Two subjects, one from each age group, received placebo
- In BHV4157-108, single doses of troriluzole (280, 560, and 840 mg) were evaluated in 30 healthy subjects for safety, tolerability, pharmacokinetics, and dose proportionality. Placebo was administered in 21 subjects
- For all results described, subjects received study drug or placebo under fasting conditions
- Plasma concentrations of the prodrug troriluzole and its active metabolite, riluzole, were determined using liquid chromatography with tandem mass spectrometry (LC-MS/MS)
- Clinical laboratory tests, vital signs, electrocardiogram (ECG) recordings, and Sheehan Suicidality Tracking Scale (S-STS) assessments were performed at screening and study exit
- Pharmacokinetic parameters were determined using standard non-compartmental analysis

METHODS AND RESULTS

Safety and Tolerability

- Incidence of adverse events did not increase with dose escalation
- The dose range for safety assessment was increased to 840 mg in BHV4157-108 after safety criteria were met in previous studies. A maximum tolerated dose was not identified
- None of the adverse events were considered above moderate severity. The most common adverse events (more than 1 subject experienced the event in at least 1 study) across the studies are described in **Table 1**
- Age ≥65 years did not meaningfully affect safety, tolerability, or pharmacokinetics of riluzole (BHV4157-103) with consideration of the small sample size
- There were no clinically meaningful trends or treatment-related findings for vital signs, ECGs, or S-STS changes from baseline

Table 1. Frequency of Common Adverse Events Across Studies

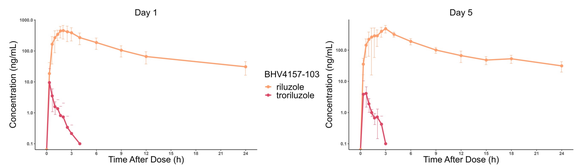
	BHV4157-101		BHV4157-103		BHV4157-108	
Event[a]	Troriluzole (n=58)	Placebo (n=20)	Troriluzole (n=8)	Placebo (n=2)	Troriluzole (n=30)	Placebo (n=21)
Headache	3	4	0	0	6	1
Somnolence	0	1	3	0	1	0
Dizziness	1	0	1	0	5	0
Infrequent bowel movements	2	0	0	0	0	0
Nausea	0	0	1	0	1	0
Neck pain	1	1	0	0	0	0
Hot flush	0	0	0	0	2	0

[a]Event category was only included if more than 1 subject experienced the event in at least one study.

Pharmacokinetic Properties of Troriluzole

- Troriluzole concentrations were only assessed in studies BHV4157-101 and BHV4157-103
- Troriluzole C_{max} was 5.4 ng/mL after a single 280 mg dose, while riluzole C_{max} was 510.4 ng/mL at the same dose, indicating that troriluzole is quickly converted to riluzole
- Troriluzole remained low and transient after multiple repeat 280 mg doses administered daily for 5 days (**Figure 1**)

Figure 1. Concentration-Time Profiles After Multiple Dose Troriluzole Administration



Pharmacokinetic Properties of Riluzole (SAD)

- Riluzole plasma exposure increased following oral administration of increasing single doses (therapeutic doses are summarized in **Table 2**)
- Under single dose, fasting conditions, riluzole concentrations at 24 hours after dosing averaged < 5% of peak concentrations
- The T½ of riluzole following administration of troriluzole is approximately 12 hours, consistent with that of generic riluzole

Table 2. Riluzole Single Dose Pharmacokinetic Parameters at Clinical Doses

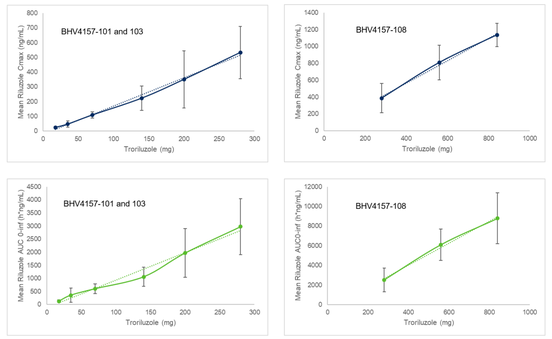
Parameter	200 mg (n=6)[a]	280 mg (n=10)[b]
$AUC_{0\text{-}inf}$ (h*ng/mL)	1771.50 (47.0%)	2297.14 (48.3%)
C_{max} (ng/mL)	307.26 (55.5%)	358.35 (44.6%)
T_{max} (h)	2.75 (1.67-4)	2.59 (1.43-4.14)
$T_{½}$ (h)	9.15 (25.7%)	11.97 (18.9%)

[a]Study BHV4157-101
[b]Study BHV4157-108
Note: $AUC_{0\text{-}inf}$, C_{max}, $T_{½}$ are displayed as geometric mean (CV%) and T_{max} is displayed as median (range)

Dose Proportionality

- Riluzole dose proportionality of $AUC_{0\text{-}inf}$ and C_{max} was analyzed following single troriluzole doses at 17.5, 35, 70, 140, 200, and 280 mg (BHV4157-101 and 103). Further analysis was performed using the power model with mixed procedures for doses at 280, 560, and 840 mg (BHV4157-108)
- Riluzole was approximately dose proportional across the studied dose range (17.5 to 840 mg single doses) (**Figure 2**)

Figure 2. Riluzole Mean C_{max} and $AUC_{0\text{-}inf}$ (±SD) of Rising Doses

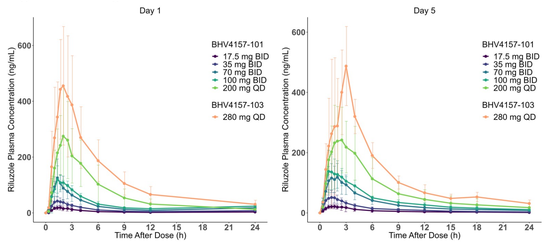


Solid lines represent riluzole PK parameters; dotted lines represent linearity (slope of dose proportionality), AUC0-24 is reported for riluzole in BHV4157-103 (bottom left panel)

Pharmacokinetic Properties of Riluzole (MAD)

- $AUC_{0\text{-}12}$ and C_{max} were both higher when the drug was administered as 200 mg once daily (QD) rather than 100 mg twice daily (BID) (**Figure 3**), supporting once daily dosing
- Riluzole C_{max} remained relatively constant when administered as 280 mg troriluzole over 5 days; Day 1 C_{max} was 510.4 ng/mL and Day 5 C_{max} was 481.7 ng/mL

Figure 3. Rising Dose Riluzole Concentration-Time Profiles



- Accumulation ratios calculated from AUC and C_{max} were similar between 200 mg QD and 280 mg QD groups (**Table 3**)
- In Study BHV4157-103, riluzole steady state was achieved within 5 consecutive days of troriluzole 280 mg QD administration
- Little or no riluzole accumulation was observed and the pharmacokinetics appeared linear
- Repeat dose administration of troriluzole was associated with reduced riluzole variability of C_{max} (200 mg QD = 41.2% and 280 mg QD = 31.6%) relative to generic riluzole (70% with standard 50 mg dose)

Table 3. Riluzole Steady State (Day 5) Pharmacokinetic Parameters at Clinical Doses

Parameter	200 mg QD (n=6)[a]	280 mg QD (n=6)[b]
$AUC_{0\text{-}T\ ss}$ (h*ng/mL)	1624.42 (46.4%)	2856.33 (28.9%)
$C_{max\ ss}$ (ng/mL)	266.28 (41.2%)	481.73 (31.6%)
RAUC	1.22 (14.4%)	1.15 (11.5%)
RC_{max}	0.86 (38.1%)	1.04 (16.1%)

[a]Study BHV4157-101
[b]Study BHV4157-103 (PK Population)
Note: All values are displayed as geometric mean (CV%)