014

No Clinically Relevant Effects of Hepatic Impairment on the Pharmacokinetics of Troriluzole

Rachel Rozakis, PharmD[1]; Mary Donohue, MS[2]; Heather Sevinsky, MS[2]; Bharat Awsare, MD[2]; Stephen Kaplita, MS[2]; Elizabeth Hussey, PharmD[1]; Irfan Qureshi, MD[2]; Vlad Coric, MD[2]; Richard Bertz, PhD[2]

[1] Allucent, LLC., Cary, NC, USA; [2] Biohaven Pharmaceuticals, Inc., New Haven, CT, USA

INTRODUCTION

- Troriluzole is a rationally designed, third generation prodrug of the glutamate-modulating agent riluzole
- Riluzole is a member of the benzothiazole class and was approved by the Food and Drug Administration (FDA) in 1995 for the treatment of amyotrophic lateral sclerosis (ALS)[1,2]
- Oral riluzole is limited by dose-dependent effects on liver function tests. Approximately 8% of riluzole-treated patients experience elevations in serum alanine aminotransferase (ALT) levels >3x above the upper limit of normal (ULN)[3]
- In contrast, clinical trials for troriluzole showed a lower incidence (2.6%) of >3x ULN ALT elevations in over 1,300 subjects
- Following oral riluzole, subjects with mild or moderate hepatic impairment (HI) displayed 1.7- and 3-fold higher total riluzole exposures, respectively, compared to normal hepatic function[3]
- Troriluzole may reduce riluzole burden on the liver, due to troriluzole's ability to bypass first pass hepatic metabolism
- Clinical study BHV4157-104 investigated the effects of HI on the pharmacokinetics of troriluzole

OBJECTIVE

- The objective of study BHV4157-104 was to determine the effect of moderate hepatic impairment on the single dose pharmacokinetics of riluzole after administration of troriluzole

METHODS OVERVIEW

- BHV4157-104 was a Phase 1, single-dose, open-label study conducted in 8 subjects with moderate HI (Group 1, Child-Pugh score 7-9 points), and 8 subjects with normal hepatic function (Group 2). All subjects received a single oral 100 mg dose of troriluzole under fasted conditions. Subjects with normal hepatic function were matched to those with HI by age (± 10 years, but ≤80 years), body mass index (± 15%), and sex utilizing a mean matching strategy
- Pharmacokinetic samples were collected pre-dose and through 144 hours (Group 1) and 72 hours (Group 2) post-dose. Riluzole pharmacokinetic parameters (total and unbound) were calculated by non-compartmental analysis. For both groups, 2 additional samples were collected for unbound riluzole measurements at 1 and 12 hours post-dose
- Safety and tolerability of troriluzole were evaluated through the assessment of adverse events (AEs), clinical laboratory parameters, 12-lead safety electrocardiograms (ECGs), vital signs, physical examination, and the Sheehan Suicidality Tracking Scale (S-STS)

METHODS AND RESULTS

Pharmacokinetics Summary

- Mean plasma total riluzole concentration-versus-time curves (**Figure 1** and **Figure 2**) are presented on linear and semilog scales, respectively
- The pharmacokinetic population included all subjects who completed the study and for whom the pharmacokinetic profile was adequately characterized
- All 16 subjects completed the study and were included in the pharmacokinetic population
- Descriptive statistics of the pharmacokinetic parameters are presented for total and unbound riluzole (**Table 1**)
- The mean riluzole fraction unbound was 1.6% in healthy subjects and 2.6% in subjects with moderate hepatic impairment
- Mean riluzole exposure was similar between subjects with moderate HI and healthy subjects with normal hepatic function
- Mean unbound riluzole exposure was approximately 1.7-fold greater for $AUC_{0\text{-}inf}$ and 1.4-fold greater for C_{max} in subjects with moderate HI compared to those with normal hepatic function
- While HI increased concentrations of unbound riluzole, the effect did not cross the 2-fold threshold specified in the FDA guidance[4] that would obviate the need for a dose modification

Table 1. Descriptive Statistics for Total Riluzole and Unbound Riluzole Pharmacokinetic Parameters by Hepatic Function Group

Group	Analyte	Parameter		
		$AUC_{0\text{-}inf}$ (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)
Moderate HI	Total Riluzole	814.29 (41.72)	112.31 (43.47)	2.00 (1.33-4.00)
Healthy	Total Riluzole	731.40 (34.39)	122.43 (42.30)	2.25 (1.33-4.00)
Moderate HI	Unbound Riluzole	20.15 (54.90)	2.78 (67.55)	NC
Healthy	Unbound Riluzole	11.75 (34.21)	1.97 (44.12)	NC

$AUC_{0\text{-}inf}$ and C_{max} are presented as geometric mean (CV%). T_{max} is displayed as median (range). NC = not calculated.

Figure 1. Mean (± SD) Riluzole Plasma Concentrations by Hepatic Function Group (Linear Scale) – Pharmacokinetic Population

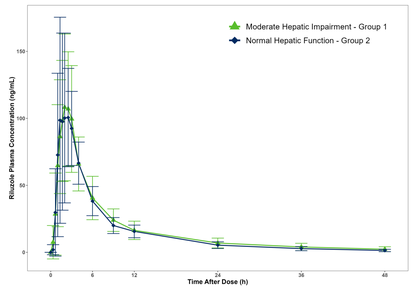
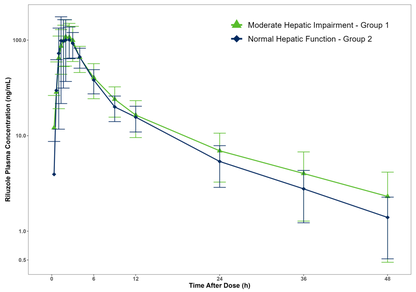


Figure 2. Mean (± SD) Riluzole Plasma Concentrations by Hepatic Function Group (Semilog Scale) – Pharmacokinetic Population



Cohort Comparison (Moderate Hepatic Impairment versus Healthy Normal Subjects)

- A general linear model (GLM) procedure in SAS was utilized to perform analysis of variance (ANOVA) on ln-transformed $AUC_{0\text{-}inf}$ and C_{max} at the alpha level of 0.05. The model included hepatic group as a fixed effect
- The ratios (Moderate HI/Normal Healthy Subjects) and 90% geometric confidence intervals (CI) were calculated according to ANOVA results for $AUC_{0\text{-}inf}$ and C_{max} (total and unbound riluzole; **Table 2** and **Table 3**, respectively)
- No clinically meaningful differences were observed between hepatic function groups in the mean total riluzole exposure ($AUC_{0\text{-}inf}$ and C_{max}) following oral administration of troriluzole, with $AUC_{0\text{-}inf}$ and C_{max} exposure in subjects with moderate HI within approximately 10% of those observed in subjects with normal hepatic function (Moderate/Normal)

Table 2. Ratios (Moderate Hepatic Impairment/Normal) and 90% Geometric Confidence Intervals of Plasma Pharmacokinetic Parameters for Total Riluzole

Parameter (unit)	Ratio Moderate/Normal[a] (%)	90% Geometric CI[b]	
		Lower (%)	Upper (%)
$AUC_{0\text{-}inf}$ (h*ng/mL)	111.33	80.45	154.08
C_{max} (ng/mL)	91.74	63.88	131.74

[a] Calculated using least squares means according to the formula: $exp^{(DIFFERENCE)} * 100$
[b] 90% Geometric CI calculated according to the formula: $exp(DIFFERENCE \pm t_{(dfResidual)} * SE_{DIFFERENCE}) * 100$

Table 3. Ratios (Moderate Hepatic Impairment/Normal) and 90% Geometric Confidence Intervals of Plasma Pharmacokinetic Parameters for Unbound Riluzole

Parameter (unit)	Ratio Moderate/Normal[a] (%)	90% Geometric CI[b]	
		Lower (%)	Upper (%)
$AUC_{0\text{-}inf}$ (h*ng/mL)	171.47	117.16	250.96
C_{max} (ng/mL)	141.29	88.89	224.58

[a] Calculated using least squares means according to the formula: $exp^{(DIFFERENCE)} * 100$
[b] 90% Geometric CI calculated according to the formula: $exp(DIFFERENCE \pm t_{(dfResidual)} * SE_{DIFFERENCE}) * 100$

Safety and Tolerability

- There were no deaths, serious adverse events (SAEs), severe AEs, or AEs that led to discontinuation
- 3 (18.8%) subjects with normal hepatic function experienced 4 treatment-emergent adverse events (TEAEs), including 2 subjects reporting somnolence and 1 subject reporting increased blood pressure and heart rate
- All TEAEs were mild and considered related to study treatment. All TEAEs resolved by the end of the study
- There were no clinically meaningful trends in laboratory values. No subjects had ALT, alkaline phosphatase (ALP), or aspartate aminotransferase (AST) values >3x ULN or total bilirubin values >2x ULN
- There were no clinically meaningful trends or treatment-related findings for vital signs, ECGs, or S-STS changes from baseline

CONCLUSIONS

1. There was no clinically meaningful effect of moderate hepatic impairment on the pharmacokinetics of total riluzole exposure following administration of 100 mg troriluzole; exposures in subjects with moderate hepatic impairment were within approximately 10% of exposures in subjects with normal hepatic function
2. Unbound riluzole exposure was approximately 1.7-fold greater for $AUC_{0\text{-}inf}$ and 1.4-fold greater for C_{max} in subjects with moderate hepatic impairment compared to subjects with normal hepatic function
3. A single dose of 100 mg troriluzole was well tolerated in subjects with moderate hepatic impairment and in those with normal hepatic function. There were no clinically meaningful trends in laboratory values, nor any incidence of liver enzyme values >3x the ULN

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

References: 1. Lacomblez L. *Lancet (London England)*. 1996; 347(9013): 1425-1431; **2.** Nightingale SL. *JAMA*. 1995; 274(14): 1109; **3.** Covis Pharmaceuticals. *Rilutek® USPI*. 2022; **4.** US FDA. Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact of Dosing and Labeling. 2003. Available from: https://www.fda.gov/media/71311/download.

To download a copy of this poster, scan QR code.

Presented at the American Academy of Neurology 2024 Annual Meeting
April 13-18, 2024 • Denver, Colorado, USA

Presenter: Heather Sevinsky, MS
heather.sevinsky@biohavenpharma.com