Assessing Effects of BHV-0223 40 mg Zydis® Sublingual Formulation and Riluzole 50 mg Oral Tablet on Liver Function Test Parameters Utilizing DILIsym®

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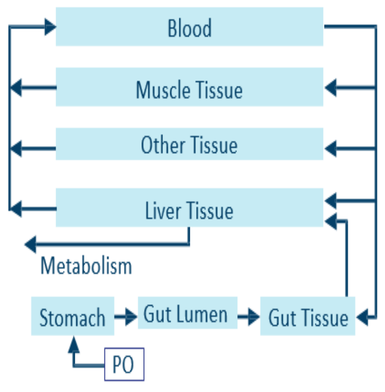
1. Premise

- Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by the death of motor neurons that leads to progressive muscle weakness and difficulties in speaking, swallowing, and breathing.
- Riluzole prolongs survival and time to tracheostomy in patients with ALS.
- Approximately 50% of patients receiving riluzole oral tablets experience elevated alanine transaminase (ALT) levels, with 8% above 3 upper limit of normal (ULN) and 2% above 5 x ULN.
- BHV-0223 is a novel 40 mg sublingually dissolving Zydis® formulation of riluzole that is bioequivalent to the riluzole 50 mg oral tablet formulation.
- Because of its sublingual route of administration, BHV-0223 bypasses first-pass metabolism, achieving adequate drug concentrations with diminished drug burden and potentially less risk of liver toxicity.
- This study quantitatively and mechanistically compared the liver toxicity potential of oral riluzole versus BHV-0223, combining clinical and mechanistic data, using DILIsym®.

2. Methods

- DILIsym is a validated multi-scale computational model that supports evaluation of liver toxicity risks.
- Oral riluzole (50 mg twice daily [BID] for 12 weeks) and sublingual riluzole (40 mg BID for 12 weeks) were simulated by combining a physiologically-based pharmacokinetic (PBPK) modelling representation of riluzole with mechanistic liver toxicity parameters derived from *in vitro* data.
- The DILIsym PBPK model framework used for riluzole consists of a compartmental model of the body with compartments for blood, gut, liver, muscle, and other tissues (**Figure 1**).

Figure 1. PBPK model structure within DILIsym. (PO, orally).

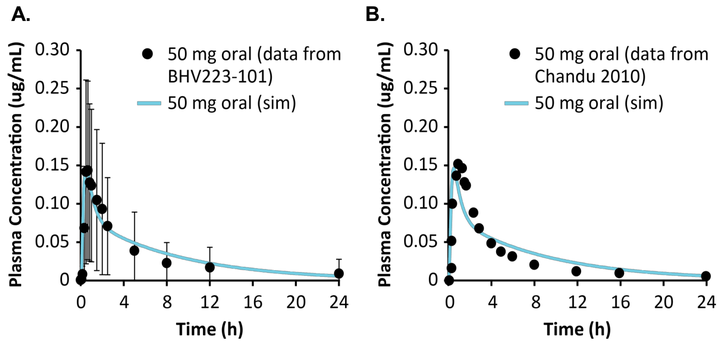


3. Results

PBPK Representation

- DILIsym simulations reasonably captured the plasma PK of riluzole (**Figure 2**).
- PK data were used to estimate the portion of sublingual riluzole that is absorbed via the oral mucosa and the portion that is swallowed and passes through the gastrointestinal (GI) tract. Simulated plasma concentrations after a sublingual dose were conducted, assuming a variable fraction of the dose is absorbed via the oral mucosa.
- Simulations in which 0% of a sublingual dose of riluzole was absorbed via the oral mucosa and 100% passed through the GI tract underestimated observed plasma concentrations.

Figure 2. Simulated (lines) and observed (symbols) riluzole concentrations after a single 50 mg oral dose for (A) observed data from the phase 1 study of BHV-0223 and (B) data reported in Chandu et al (*Anal Bioanal Chem*. 2010)



Toxicity Simulations

- SimPops are simulated individuals with parameter variability designed to reflect appropriate biochemical and anthropometric ranges. For this study, a SimPops (N=285) with variability in mitochondrial function, caspase activation (apoptosis), bile acid concentrations, and oxidative stress was utilized.
- Simulations were conducted in SimPops with median and high PK parameterizations (representing median and high plasma riluzole exposure) combined with default and high riluzole liver-to-blood partition coefficients (liver K_b).
- No ALT elevations >3 x ULN were predicted for either dosing protocol (oral or sublingual) with median PK (**Table 1**).
- In simulations with high PK and high liver exposure (K_b 10), the predicted incidence of ALT elevations was higher for oral dosing (11 of 285 individuals) vs. sublingual dosing (4 of 285).

Table 1. Simulated frequency of ALT elevations in SimPops

Riluzole dose and duration	DILIsym parameter settings	Simulated ALT >3 × ULN[a]	Simulated ALT >5 × ULN[a]
Oral 50 mg once daily for 12 weeks	Median PK, liver K_b 10	0/285	0/285
	High PK, liver K_b 10	11/285	3/285
Sublingual 40 mg once daily for 12 weeks	Median PK, liver K_b 10	0/285	0/285
	High PK, liver K_b 10	4/285	2/285

[a]ULN in DILIsym is 40 U/L. ALT, alanine aminotransferase; K_b, liver-to-blood partition coefficient; PK, pharmacokinetic; ULN, upper limit of normal.

4. Conclusions

- While both deliver bioequivalent exposures, sublingual BHV-0223 theoretically has less risk of liver toxicity compared to riluzole oral tablets. DILIsym modeling demonstrated that sublingual BHV-0223 confers diminished rates of liver toxicity compared to oral tablets of riluzole, consistent with having a lower overall dose of riluzole and bypassing first-pass liver metabolism.
- Key determinants of the simulated outcomes included liver exposure relative to plasma. Physiologically reasonable assumptions regarding liver exposure confirmed the propensity for oral riluzole tablets to confer elevations in liver function tests at rates that are comparable to that observed clinically, thus validating the DILIsym representation of oral riluzole.

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