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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Background

- 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 via a number of potential mechanisms, including reduction of glutamate excitotoxicity.
- Riluzole can cause dose-related abnormalities in liver function tests.
- Approximately 50% of patients receiving riluzole oral tablets experience elevated alanine transaminase (ALT) levels, with 8% above 3 x upper limit of normal (ULN) and 2% above 5 x ULN.
- BHV-0223 is a novel investigational 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.
- DILIsym® (DILIsym Services, Inc, Research Triangle Park, NC) is a validated multi-scale computational model that supports evaluation of liver toxicity risks.

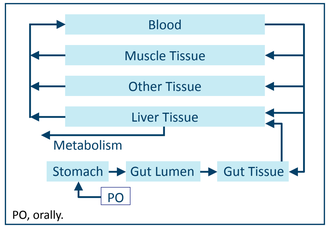
Objective

- To quantitatively and mechanistically compare the liver toxicity potential of oral riluzole versus BHV-0223, combining clinical and mechanistic data, using DILIsym.

Methods

- 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



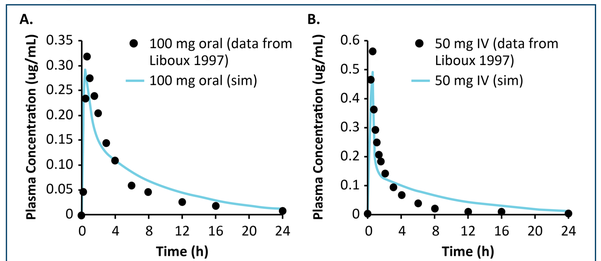
- The PBPK representation of riluzole was based on available data for BHV-0223 and published studies of riluzole.
  - Data on plasma riluzole exposure from a published pharmacokinetics (PK) study of riluzole (single 50 mg intravenous [IV] dose and single 100 mg oral dose in healthy volunteers) were used to optimize the model parameters.
  - The model was validated against clinical data from a completed phase 1 trial and previously published trials in healthy volunteers, including the PK study of ascending doses of riluzole (25, 50, or 100 mg dose BID).
- 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 35 mg sublingual dose were conducted, assuming variable amounts absorbed via the oral mucosa.
- Simulations were conducted in DILIsym SimPops and SimCohorts to assess the hepatotoxic potential of oral and sublingual riluzole.
  - SimPops are collections of simulated individuals with parameter variability designed to reflect appropriate biochemical and anthropometric ranges.
  - SimCohorts are relatively small groups of simulated individuals consisting of a subset of individuals from existing SimPops generated for screening and sensitivity analysis purposes.
  - For this study, a SimPops (N=285) with variability in mitochondrial function, caspase activation (apoptosis), bile acid concentrations, and oxidative stress was utilized.
  - The SimCohorts utilized for this study included the baseline human and 13 sensitive individuals and 2 individuals with low sensitivity in the areas of oxidative stress, mitochondrial dysfunction, bile acid transport inhibition, and combined bile acid transport inhibition and mitochondrial dysfunction.
- Simulations were performed 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).
  - PK parameterizations were based on variability observed in the completed BHV-0223 phase 1 study and were consistent with exposures 1 standard deviation above the median level.
  - K_b values were based on available in vitro data and in silico calculations; the high K_b value represented the highest value calculated from in vitro data.

Results

PBPK optimization

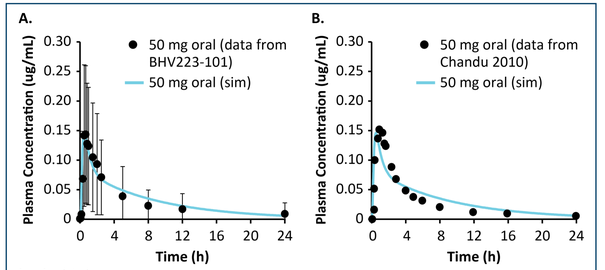
- The DILIsym simulations reasonably captured the plasma PK of riluzole (**Figures 2-3**).

Figure 2. Simulated (lines) and observed[a] (symbols) plasma concentrations of riluzole following (**A**) a single 100 mg oral dose and (**B**) a single 50 mg IV dose



[a]Observed data are from Liboux et al (*J Clin Pharmacol*. 1997).
IV, intravenous; sim, simulated.

Figure 3. Simulated (lines) and observed (symbols) plasma concentrations of riluzole 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)



sim, simulated.

- Simulations in which 0% of a 35 mg sublingual dose of riluzole was absorbed via the oral mucosa and 100% passed through the GI tract underestimated observed plasma concentrations following a single 35 mg sublingual dose.

Riluzole toxicity simulation

- In the SimPops simulations, no ALT elevations >3 × ULN were predicted for either dosing protocol (oral or sublingual) with median PK and high or default liver exposure assumptions (**Table 1**).

Table 1. Simulated frequency of ALT elevations in SimPops administered riluzole

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.

- In the simulation with high PK and high liver exposure, the predicted incidence of ALT elevations was higher for oral dosing (11 of 285 individuals) vs sublingual dosing (4 of 285).
- Findings from the SimCohorts simulations were similar: no ALT elevations were predicted with the default liver K_b assumption combined with either median or high PK parameter; elevations were predicted only with the higher liver K_b assumptions (**Table 2**).

Table 2. Simulated frequency of ALT elevations in SimCohorts administered riluzole

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	0/16	0/16
	High PK, liver K_b 10	3/16	1/16
	Median PK, liver K_b 35	3/16	1/16
	High PK, liver K_b 35	16/16	16/16
Sublingual 40 mg once daily for 12 weeks	Median PK, liver K_b 10	0/16	0/16
	High PK, liver K_b 10	1/16	1/16
	Median PK, liver K_b 35	1/16	1/16
	High PK, liver K_b 35	16/16	15/16

[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.

- In both simulations with high PK parameters and liver K_b of 10 and in simulations with median PK and liver K_b of 35, 3 of 16 simulated individuals with oral dosing and 1 of 16 individuals with sublingual dosing showed ALT elevations.
- With high PK parameters and the highest liver K_b value of 35, all simulated individuals in both dosing protocols had elevated ALT 3 × ULN.

Conclusions

- Sublingually administered BHV-0223 is associated with meaningful levels of mucosal absorption of riluzole, based on PBPK modeling.
- While both deliver bioequivalent exposures, sublingual BHV-0223 theoretically has less risk of liver toxicity compared to riluzole oral tablets. This advantage is supported by DILIsym, which combines a mechanistic, quantitative representation of hepatotoxicity with inter-individual variability in both susceptibility and liver exposure.
- DILIsym modeling predicted that sublingual BHV-0223 would confer 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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