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A Pharmacokinetic Bioequivalence Study Comparing Sublingual Riluzole (BHV-0223) and Oral Tablet Formulation of Riluzole in Healthy Volunteers

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Abstract

Orally administered riluzole extends survival in patients with amyotrophic lateral sclerosis, although it has significant shortcomings (eg, adverse events, dysphagic patients) that limit its utility. BHV-0223 is a Zydis-based orally disintegrating formulation of riluzole designed for sublingual administration that addresses the limitations of conventional tablets. This study assessed the bioequivalence between 40-mg BHV-0223 and standard 50-mg oral riluzole tablets, and the food effect on BHV-0223 pharmacokinetics in healthy volunteers. Overall, 133 healthy subjects received BHV-0223 and riluzole tablets under fasted conditions. Geometric mean ratios for the area under the plasma concentration–time curve (AUC) from time zero to time of last nonzero concentration ($AUC_{0\text{-}t}$) (89.9%; confidence interval [CI], 87.3%–92.5%), AUC from time zero to infinity ($AUC_{0\text{-}\infty}$) (89.8%; CI, 87.3%–92.4%), and maximum observed concentration (112.7%; CI, 105.5%–120.4%) all met bioequivalence criteria (80%–125%). Subsequently, 67 subjects received BHV-0223 under fed conditions. The geometric mean ratios of $AUC_{0\text{-}t}$ (91.2%; CI, 88.1–94.3%), and $AUC_{0\text{-}\infty}$ (92.0%; CI, 89.0–95.1%) were similar, but maximum observed concentration ratios were not within bioequivalence criteria. BHV-0223 was well tolerated. This study demonstrated that 40-mg sublingual BHV-0223 is bioequivalent to 50-mg oral riluzole tablets.

Keywords

amyotrophic lateral sclerosis, bioequivalence, pharmacokinetics, riluzole, sublingual

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig disease, is a progressive, neurogenerative disorder characterized by the degeneration of motor neurons in the brain and spinal cord,[1–3] with a prevalence of approximately 3 to 5 per 100,000 persons.[4] The etiology and pathogenesis of ALS are unknown, although a number of hypotheses have been formulated. One hypothesis has been linked to glutamate, with destruction of motor neurons triggered through excessive activation of glutamate receptors at the synaptic cleft.[5] ALS begins with focal weakness but spreads to involve most voluntary muscles, including the accessory muscles involved in respiration (ie, the diaphragm).[1] The initial clinical presentation is heterogeneous and depends on the specific neuronal substrates (ie, upper motor neurons in the cerebral cortex vs lower motor neurons in the brainstem or spinal cord).[1] Approximately 70% of cases begin with limb weakness,[6] while 30% begin with bulbar weakness,[7] which generally presents as dysphagia and dysarthria.[6] Regardless of the initial presentation, people with ALS experience increasing difficulties with mobility, speaking, swallowing, and breathing.[6]

The US Food and Drug Administration approved riluzole in 1995 (in the form of Rilutek 50-mg oral

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tablets, twice daily) for the treatment of patients with ALS.[8] Although the mechanism of action of riluzole has not been fully elucidated, its pharmacological properties include an inhibitory effect on glutamate release, inactivation of voltage-dependent sodium channels, and disruption of intracellular events that follow transmitter binding at excitatory amino acid receptors. Riluzole is well absorbed (approximately 91%), with a mean bioavailability of approximately 60%.[9] A high-fat meal decreases the absorption of riluzole in the gastrointestinal system, thus resulting in lower plasma levels.[9] Riluzole is metabolized mainly by the hepatic enzyme cytochrome P450 1A2 (CYP1A2), in a nicotinamide adenine dinucleotide phosphate–dependent reaction. This reaction forms N-hydroxyriluzole,[10] which may be pharmacologically active.[11] Patients with hepatic impairment therefore have diminished riluzole clearance.[12] Furthermore, tobacco smoking induces CYP1A2, thus accelerating riluzole clearance, potentially decreasing the effectiveness of riluzole.[12] Riluzole also showed weak inhibitory effects on CYP1A2. Riluzole undergoes biotransformation through glucuronidation by uridine 5′-diphospho-glucuronosyltransferase to a lesser extent,[12] and is primarily eliminated via urine.[13]

Clinical studies in patients with ALS have shown that riluzole reduced risk of death or tracheostomy by 35% after 18 months of treatment.[14] However, the majority of patients with ALS will eventually experience dysphagia,[15,16] which could lead to issues with riluzole in its current tablet formulation such as safety concerns (eg, choking, aspiration) and misuse of riluzole (eg, chewing, crushing, administering with food).[16,17] Swallowing liquids can also be difficult for patients with ALS. Changing the consistency of liquids may help facilitate swallowing; however, a large majority of patients do not accept the use of thickeners for liquids.[16] Other limitations to the administration of riluzole as a tablet formulation include the prescribing information for riluzole, which indicates that tablets should be taken at least 1 hour before or 2 hours after a meal to avoid a food-related decrease in bioavailability, which imposes a requirement of fasting. Hepatic dose-related adverse events (AEs) are also a limitation to the current riluzole formulation.[18,19] In previous dose-ranging studies, riluzole was associated with transaminase abnormalities that emerged at daily doses of 100 mg and higher.[14,20] Furthermore, riluzole tablets have demonstrated marked pharmacokinetic (PK) variability that is thought to be associated with outlier concentrations that are sufficiently high to potentially alter the expected safety and tolerability in some patients.[14] Variable absorption through the gastrointestinal tract and first-pass hepatic metabolism may underpin this PK variability.

BHV-0223 is an oral disintegrating tablet formulation of riluzole administered sublingually for the treatment of patients with ALS and aims to address the key limitations associated with the current riluzole tablet formulation. BHV-0223 is manufactured with a proprietary lyophilization process (using Zydis technology[21]) that is designed to optimize pharmaceutical and PK properties, specifically to (1) enhance mucoadhesive properties, allowing for efficient absorption while limiting dispersion after sublingual placement; (2) provide rapid dissolution, within seconds, upon oral placement; and (3) offer adequate handling properties.

Here, we present results from a phase 1 study conducted to evaluate the bioequivalence between the new 40-mg formulation of riluzole for sublingual administration, BHV-0223, and the approved oral 50-mg tablet formulation of riluzole, in healthy volunteers. The effect of food on the PK of BHV-0223, and the safety and tolerability of BHV-0223 were also assessed.

Methods

Study Conduct

The clinical study protocol was reviewed by an independent ethics committee, Institutional Review Board Services, located in Aurora, Ontario, Canada. All subjects completed a written informed consent form before the initiation of study procedures. This study was conducted at the inVentiv Clinical Research Facility (2 locations in Québec, Canada) and was in compliance with Good Clinical Practice guidelines as referenced in the International Council for Harmonization guidelines, and the code of ethics of the World Medical Association's Declaration of Helsinki.

Study Design

The lowest riluzole dose of BHV-0223 sublingual formulation, projected to be bioequivalent to 50-mg riluzole tablets, was determined through a single-dose exploration study of BHV-0223 in healthy subjects, the data from which were used to develop a basic population PK model.[22] The validated population PK model was then used to simulate 50 bioequivalence studies for different doses of BHV-0223 ranging from 38.5 to 46 mg with varied sample sizes. Based on the simulations performed, a 40-mg dose of riluzole using the sublingual oral disintegrating tablet formulation (BHV-0223) formulation was selected to perform the bioequivalence and food effect study.

This single-center, single-dose, open-label, phase 1, bioequivalence and food effect study was designed to be conducted in 3 sequential parts (Figure 1). The objectives of this study were to compare the rate and extent of absorption of 40-mg BHV-0223 vs a 50-mg riluzole

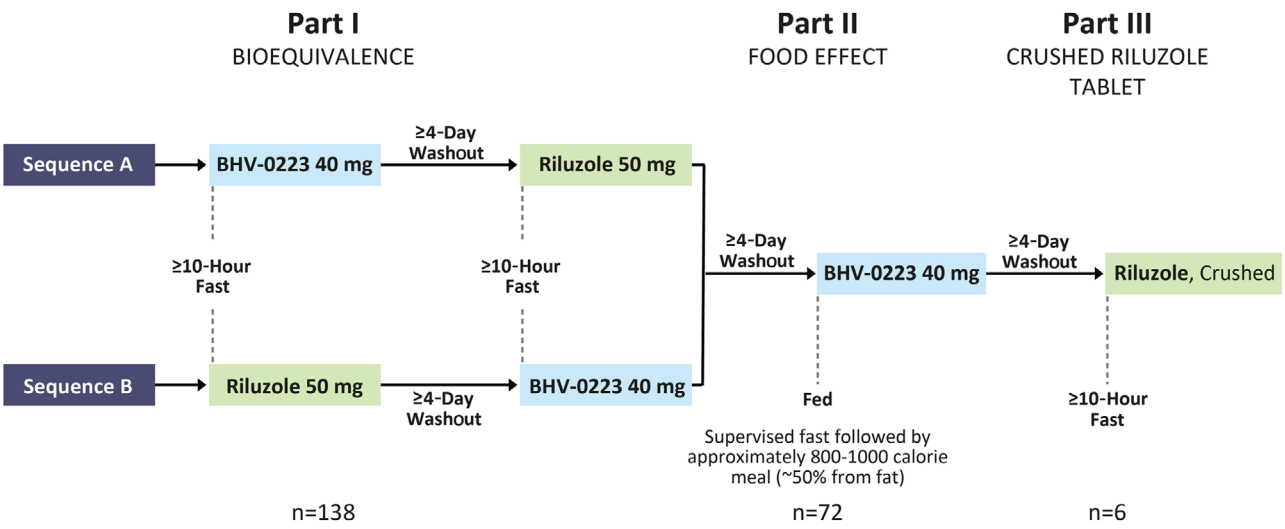

Figure 1. Study design. After completing Part I, the Part II subset of subjects were selected based on convenience (eg, the first 72 subjects who were able to commit to attending an additional dosing period). Of the subjects included in Part II, 6 were planned to be included in Part III and were selected based on convenience.

tablet under fasted conditions (Part I), and to evaluate the effect of food on the PK of BHV-0223 in healthy volunteers (Part II). Other objectives were to assess the PK of sublingual absorption of a crushed riluzole tablet (Part III) and the safety and tolerability of BHV-0223 in healthy volunteers. The systemic metabolite profiles of riluzole when administered orally (riluzole tablet) and sublingually (BHV-0223) were also assessed.

Part I. A total of 138 subjects were randomized equally into 1 of the 2 treatment sequences under fasted conditions (no food from ≥10 hours before to ≥4 hours after dosing). A single 40-mg dose of BHV-0223 followed with a single 50-mg oral dose of a riluzole tablet with 240 mL of water, or a single 50-mg oral dose of a riluzole tablet with 240-mL water followed with a single 40 mg dose of BHV-0223. There was a washout period of 4 days between treatments (Figure 1).

Part II. The first 72 subjects enrolled in Part I of the study who were able to commit to attending an additional dosing period were enrolled in Part II and received BHV-0223 under fed conditions (Figure 1). After a supervised fast of ≥10 hours, subjects were served a high-fat, high-caloric meal (approximately 800–1000 calories with approximately 50% of total caloric content of the meal derived from fat; comprising 2 eggs fried in butter, 2 slices of toast with butter, 2 strips of bacon, approximately 120 g of hash brown potatoes, and 200 mL of whole milk). Subjects were required to start their meal as soon as it was served and complete it within 30 minutes. Drug administration occurred 30 ± 1 minutes after the meal had been started.

Part III. Six subjects were planned to be enrolled. From the first 72 subjects randomized in Part I, 12 subjects were randomly preselected based on their availability. Of these, 2 subjects had already been withdrawn in Part I. Out of the remaining 10 subjects, 6 subjects were randomly selected to receive a single dose of a crushed 50-mg riluzole tablet placed under the tongue for 120 seconds under fasted conditions (no food from ≥10 hours before to ≥4 hours after dosing), followed by discarding (spitting) any residue and rinsing the mouth 3 times with water.

Subjects

Key inclusion criteria included subjects aged ≥18 years with no tobacco use within 3 months before screening, body mass index >18.5 and <30.0 kg/m^2, body weight ≥50 kg for men and ≥45 kg for women, and able to provide informed consent. Key exclusion criteria included the presence of dentures, braces, or oral piercings at the time of dosing, clinically significant medical history, concurrent diseases, or any physical findings in the mouth or tongue that, in the opinion of the investigator, would be likely to interfere with successful completion of dosing procedures, or physical and/or abnormal laboratory test findings that would prevent the subject from participating in the study. No concomitant drug therapies were permitted during the study except those required for medical management of an AE. Hormonal contraceptive use was allowed and documented.

Procedures

Subjects were confined to the clinical research facility from at least 11 hours before drug administration until after the 24-hour postdose blood draw, in each period. Subjects were asked to come back to the clinical facility for a subsequent blood draw at 48 hours.

For the quantitation of plasma riluzole and its metabolites, riluzolamide, N-OH-riluzole-O-glucuronide, and N-OH-riluzole, 6-mL blood samples were drawn before drug administration, and 0.083, 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, and 48 hours postdose for each drug treatment. Urine samples were collected for 12 subjects in Part I only (selected based on availability and subject numbering) in 4 periods: ≤15 minutes before dosing and between 0 to 4 hours, 4 to 8 hours, and 8 to 12 hours postdose for analysis of riluzole N-glucuronide, N-hydroxyriluzole, and N-OH-riluzole-O-glucuronide.

An oral assessment and local tolerability assessment was performed at screening, before, and at approximately 60 minutes after each dosing. Any alteration of the appearance of the tongue, palate, and buccal mucosa space was recorded. Oral safety assessment included any history of dysphagia (difficulty swallowing), dysgeusia (the distortion of the sense of taste), or burning, stinging, or tingling sensation of the mouth; stomatitis (inflammation and infection of the oral mucosa), gingivitis (inflammation of the gums leading to erythema, swelling, and bleeding); xerostomia (a dry mouth) or staining of mucosa. Severity of assessments were graded as follows: grade 0, normal mucosa; grade 1, localized mucosal erythema and/or irritation without ulceration; grade 2, generalized erythema and/or irritation and induration without ulceration; and grade 3, ulceration, with or without any other combination of signs.

Bioanalytical Methods

Concentration of riluzole in human plasma was determined using a fit-for-purpose assay employing high/ultra-performance liquid chromatography with tandem mass spectrometry detection methods that were developed and validated in accordance with good laboratory practice standards (inVentiv Health, Quebec, Canada). All concentration values below the lower limit of quantification were set to zero. The validated riluzole concentrations ranged from 500 to 500 000 pg/mL using these methods.

Similar high/ultra-performance liquid chromatography with tandem mass spectrometry detection methods were used to determine concentrations of riluzole's major metabolites in either plasma or urine. These major metabolites included riluzolamide, N-hydroxyriluzole O-glucuronide, and N-hydroxyriluzole in human plasma; and N-hydroxyriluzole, N-hydroxyriluzole-O-glucuronide, and riluzole N-glucuronide in human urine (inVentiv Health, Québec, Canada). More detailed information is available in the Supplemental Information.

Safety

Throughout the study, AEs were recorded and evaluated for duration, severity, relationship to study treatment, and seriousness. Serious AEs were defined as any event that was fatal, life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, or required medical or surgical intervention to prevent one of the above outcomes based on appropriate medical judgment. Clinical laboratory tests were performed for each subject at the time of screening, before dosing, and at study exit; serology was performed at screening only. Results were measured by and obtained from a central laboratory (Biron Medical Laboratory Inc, Brossard, Quebec, Canada). Vital signs measurements were performed at screening and study exit, and electrocardiograms and general physical examinations were performed at screening.

Pharmacokinetic Analyses

PK analyses were performed using Phoenix WinNonlin version 6.4 (Certara, Princeton, New Jersey), which was validated for bioequivalence/bioavailability studies by inVentiv Health.

Primary PK end points were area under the concentration–time curve (AUC) from time zero to last nonzero concentration ($AUC_{0\text{-}t}$), calculated by noncompartmental analysis using the linear trapezoidal model; AUC from time zero to infinity ($AUC_{0\text{-}\infty}$; extrapolated), calculated as $AUC_{0\text{-}t}+C_t/K_{el}$, where C_t is the last observed nonzero concentration and K_{el} is the elimination rate constant; and maximum observed concentration (C_{max}). Secondary PK end points were residual area, calculated as $100 \times (1\text{-}AUC_{0\text{-}t}/AUC_{0\text{-}\infty})$; time of observed C_{max}; elimination half-life ($t_{1/2\ el}$), calculated as $\log(2)/K_{el}$ using the natural logarithm; and K_{el}, calculated as the negative of the estimated slope of the linear regression of the log-transformed concentration (natural logarithm) vs the time profile in the terminal elimination phase, using ≥3 concentration points. The above parameters were calculated from plasma concentrations and metabolites: riluzolamide, N-OH-riluzole-O-glucuronide, and N-OH-riluzole. Urine concentrations of riluzole metabolites N-OH-riluzole-O-glucuronide, N-OH-riluzole, and riluzole glucuronide were used to calculate cumulative urinary excretion ($Ae_{0\text{-}t}$), maximum rate of urinary excretion, time of maximum rate of urinary excretion, and renal clearance calculated as $Ae_{0\text{-}t}/AUC_{0\text{-}t}$.

Statistical Analyses

Sample size calculations for bioequivalence evaluation were based on data from an earlier phase 1 study, assuming an expected ratio within 0.85–1.18 and an

Table 1. Subject Demographics

Characteristic	Part I (n = 138)	Part II (n = 67)	Part III (n = 6)
Age, y, mean (SD)	42.0 (13)	45.6 (12.8)	52.5 (10.2)
18–40, n (%)	68 (49)	27 (40)	1 (17)
>40, n (%)	70 (51)	40 (60)	5 (83)
Male, n (%)	69 (50)	24 (36)	4 (67)
Race, n (%)			
White	134 (97)	65 (97)	6 (100)
Black	2 (1)	0	0
Asian	2 (1)	2 (3)	0
Ethnicity			
Not Hispanic or Latino	111 (80)	52 (78)	5 (83)
Hispanic or Latino	27 (20)	15 (22)	1 (17)
Height, mean (SD), cm	167.2 (8.4)	168.1 (8.7)	167.0 (12.6)
Weight, mean (SD), kg	70.6 (11.0)	72.5 (9.5)	72.5 (10.5)
BMI, mean (SD), kg/m^2	25.2 (2.7)	25.6 (2.4)	25.9 (1.6)

BMI, body mass index; SD, standard deviation.

intra–coefficient of variation (CV) of 18% for AUC, and an expected ratio within 0.95–1.05 and intra-CV of 38% for C_{max}. Based on these calculations, 120 subjects would provide 80% power to show bioequivalence. To accommodate potential dropouts, target enrollment was 138 subjects. To evaluate a potential food effect, with an expected ratio within 0.87–1.15 and an intra-CV of 18% for AUC, with an expected ratio within 0.95–1.05 and an intra-CV of 38% for C_{max}, 60 subjects would provide 80% power to show bioequivalence of 40-mg sublingual BHV-0223 between fed and fasted states. To further accommodate potential dropouts, 72 subjects were planned for dosing under fed conditions. The sample size for Part III was determined empirically to provide qualitative data.

Univariate statistics were calculated for continuous demographic variables, plasma concentrations, and PK parameters; frequency counts and percentages were calculated for categorical demographic variables. Analysis of variance was performed on natural logarithm-transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max}, and on untransformed time to maximum concentration, K_{el}, and $t_{1/2\,el}$. Analyses were performed using general linear model procedures using SAS software (SAS Institute, Cary, North Carolina), with an α level of .05.

Bioequivalence and Food Effect Criteria

For 40-mg sublingual BHV-0223 and the 50-mg oral riluzole tablet to be considered bioequivalent, the geometric least squares (LS) means ratios and 90% confidence intervals (CIs) had to be within the recommended bioequivalence criteria (80%–125%). Similarly, no food effect would be considered if the ratios were within the bioequivalence criteria (80%–125%).

Results

Subjects

A total of 287 subjects underwent screening, of whom 160 were enrolled, and 138 subjects were dosed; 137 subjects received 1 dose of BHV-0223. One subject withdrew from Part I due to an AE (blood creatine phosphokinase increased), 1 due to noncompliance with the study drug, and 3 due to dosing irregularities. Ultimately, 133 out of 138 subjects completed both treatments in Part I. For Part II, the first 72 subjects randomized in Part I were planned to be enrolled. Four subjects were lost due to dropout or withdrawal in the course of Part I and were not replaced. One was withdrawn from the study due to an AE (rash). Therefore, 67 subjects were dosed in Part II, and all of these subjects completed Part II. For Part III of the study, 6 subjects were planned to be enrolled. All 6 subjects completed Part III (Figure S1).

A summary of demographic characteristics in each study part is shown in Table 1. Throughout all parts of the study, the majority of subjects were white (97%–100%), and the mean age ranged from 42 to 53 years. The proportion of women ranged from 36% to 67%.

Pharmacokinetic Analyses

Plasma concentrations over time for fasted BHV-0223 and fasted oral riluzole tablet are shown in Figure 2. PK parameters for these 2 treatments were generally similar (Table 2). Fasted BHV-0223 demonstrated bioequivalence to the riluzole tablets, with the geometric LS means ratios and derived geometric 90%CIs for $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max}, all falling within the standard bioequivalence criteria (Table 3). The plasma concentration–time profiles for BHV-0223

Table 2. Pharmacokinetic Parameters for BHV-0223 and the Riluzole Tablet

Parameter	Part I: Fasted Conditions		Part II: Fed Conditions	Part III: Fasted Conditions
	40-mg Sublingual BHV-0223 (n = 133)	50-mg Oral Riluzole Tablet, With Water (n = 132)	40-mg Sublingual BHV-0223 (n = 67)	50-mg Oral Riluzole Tablet, Crushed (n = 6)
$AUC_{0\text{-}t}$, mean ± SD h • ng/mL	647.51 ± 248.68	740.94 ± 338.45	572.40 ± 208.95	70.43 ± 115.84
(%CV)	(38.4)	(45.7)	(36.5)	(164.5)
$AUC_{0\text{-}\infty}$, mean ± SD h • ng/mL	670.13 ± 259.66	768.15 ± 357.63	598769.64 ± 225.56	78.48 ± 122.42
(%CV)	(38.8)	(46.6)	(37.7)	(156.0)
Residual area, mean ± SD, %	3.34 ± 1.62	3.34 ± 1.66	4.24 ± 2.29	17.77 ± 12.19
(%CV)	(48.4)	(49.8)	(54.0)	(68.6)
C_{max}, mean ± SD, ng/mL	185.01 ± 83.95	177.58 ± 105.43	68.11 ± 26.34	20.50 ± 24.59
(%CV)	(45.4)	(59.4)	(38.7)	(120.0)
t_{max}, median (min, max), h	0.66 (0.33, 1.50)	0.83 (0.33, 4.00)	2.50 (0.33, 8.00)	0.50 (0.34, 1.00)
$t_{1/2\ el}$, mean ± SD, h	10.98 ± 2.08	10.96 ± 1.97	10.92 ± 2.11	7.23 ± 4.11
(%CV)	(18.9)	(18.0)	(19.3)	(56.9)

AUC, area under the plasma concentration–time curve; $AUC_{0\text{-}t}$, AUC from time zero to last nonzero concentration; $AUC_{0\text{-}\infty}$, AUC from time zero to infinity; C_{max}, maximum observed concentration; CV, coefficient of variation; SD, standard deviation; $t_{1/2\ el}$, elimination half-life; t_{max}, time to maximum concentration.

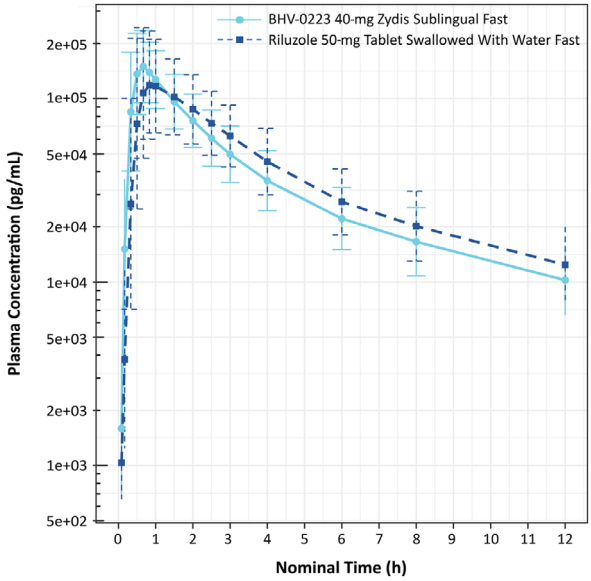

Figure 2. Mean (SD) riluzole plasma concentrations over time for 40-mg sublingual BHV-0223 and 50-mg oral riluzole tablet, under fasted conditions. SD, standard deviation.

following fed conditions (Part II) are shown in Figure 3. LS means ratios (fed vs fasted) and 90%CIs for $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ were within bioequivalence criteria, but C_{max} was reduced by 61% and delayed by approximately 1.8 hours later under fed conditions (Table 3). Mean residual area was <5% for Parts I and II (Table 2), indicating that sampling over 48 hours was sufficient for assessing riluzole PK. $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} CVs observed for BHV-0223 under fasted and fed conditions were all lower than those observed for oral fasted riluzole tablet (Table 2). The plasma concentration–time profiles for the riluzole tablet swallowed with water or crushed under fasting conditions are shown in Figure S2. Administration of a crushed riluzole 50-mg tablet sublingually for 2 minutes (Part III) without expelling/swallowing decreased the $AUC_{0\text{-}\infty}$ and C_{max} of riluzole by 94% and 90%, respectively, compared with the swallowed riluzole 50-mg tablet in Part I (Table 3). Geometric LS means ratios and 90%CIs for $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} for this comparison were all <25% (Table 3).

Pharmacokinetic Variability

CVs for $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} observed for BHV-0223 in Part I (fasted) were 38.41%, 38.75%, and 45.38%, respectively, and are consistently smaller than those measured with the riluzole tablet (45.68%, 46.56%, and 59.37%, respectively). These findings are also observed in Part II when comparing BHV-0223 under fed conditions (36.50%, 37.67%, and 38.66%, for $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and $C_{max,}$ respectively) with the riluzole tablet in Part I (Table 2). Moreover, the lower PK variability under fasted conditions is most evident in patients with the highest exposures to riluzole (eg, highest quartile) (Figure S3). This has the effect of minimizing the breadth of exposures to which subjects may be exposed relative to the riluzole tablet. Importantly, patients in the lowest quartile of exposures do not exhibit diminished exposure relative to the 50-mg riluzole tablet formulation.

Table 3. Geometric LS mean ratios and 90%CIs for $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max}

Parameter, % (90%CI)	Sublingual BHV-0223 vs Oral Riluzole Tablet (n = 132)	Sublingual BHV-0223 Fed vs Fasted (n = 67)	Riluzole Tablet Crushed vs Swallowed With Water (n = 6)
$AUC_{0\text{-}t}$	89.8 (87.3–92.5)	91.2 (88.1–94.3)	4.7 (2.2–10.0)
$AUC_{0\text{-}\infty}$	89.8 (87.3–92.4)	92.0 (89.0–95.1)	5.6 (2.9–10.7)
C_{max}	112.7 (105.5–120.4)	38.9 (36.3–41.6)	10.1 (4.2–24.5)

AUC, area under the plasma concentration–time curve; $AUC_{0\text{-}t}$, AUC from time zero to last nonzero concentration; $AUC_{0\text{-}\infty}$, AUC from time zero to infinity; C_{max}, maximum observed concentration; CI, confidence interval; LS, least squares.

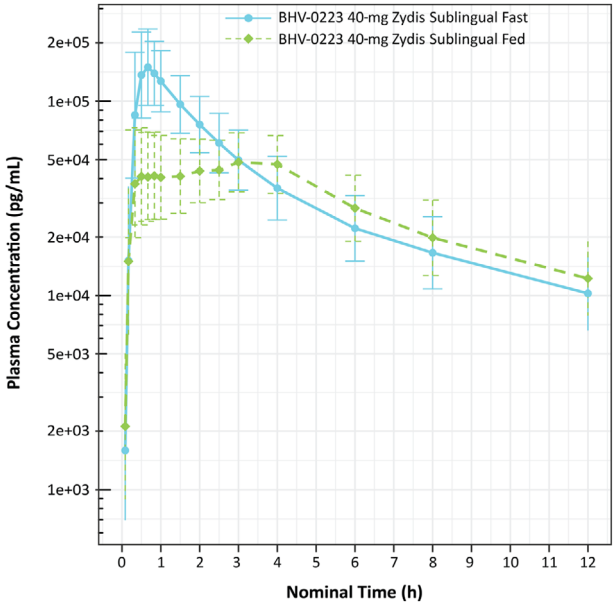

Figure 3. Mean (SD) riluzole plasma concentrations over time for 40-mg sublingual BHV-0223 under fed and fasted conditions. SD, standard deviation.

Safety

Overall, BHV-0223 was safe and well tolerated in healthy adult patients. There were no deaths or other serious AEs reported in this study. Of the 138 patients who received at least 1 dose of study medication, 29 patients experienced 44 AEs that were considered possibly related to the study medication and 116 patients experienced 176 AEs that were considered probably related to study medication. The majority (96%) of treatment-emergent AEs were mild in severity and resolved spontaneously by the end of treatment (Table 4).

The most frequently reported treatment-emergent AEs were oral hypoesthesia, followed by headache and difficulty swallowing (recorded as dysphagia), all mild and transient. The majority of patients (81%; n = 111) dosed with BHV-0223 in the fasted state reported oral hypoesthesia with a median duration to resolution of 34 minutes (range, 1–91 minutes). None of the subjects experienced oral hypoesthesia after receiving a riluzole tablet swallowed with water (Table 4). Compared with the whole tablet, oral hypoesthesia was experienced by all 6 subjects who received crushed riluzole tablets, with a median duration to resolution of 34 minutes (range, 1–91 minutes). Fourteen subjects reported a sensation of difficulty swallowing after fasted or fed BHV-0223, with a median duration to resolution of 30 minutes (range, 1–58 minutes). Despite the sensation of having difficulty swallowing (dysphagia), there were no reports of coughing, choking, or aspiration among these subjects.

There were 2 withdrawals from the study due to AEs, 1 due to blood creatine phosphokinase increasing 6 days after receiving an oral riluzole tablet (Part I) and 1 due to rash 15 minutes after receiving fasted BHV-0223 (occurred after completing dosing in Part I and was withdrawn before Part 2). Both AEs were considered mild in severity and possibly related to study medication by the investigator, and both resolved spontaneously without treatment.

No clinically meaningful changes were observed in laboratory values, vital signs, physical examinations, or electrocardiograms during the study. Abnormal blood creatine phosphokinase was reported as an AE in 2 subjects, considered mild in severity, possibly related to study medication, and resolved without treatment. No subjects had elevated liver transaminases >2× the upper limit of normal (ULN). For the oral safety and local tolerability assessments, 4 subjects had localized mucosal erythema and/or irritation without ulceration, a finding that was present at baseline in 3 subjects and 2 subjects had ulceration that was present before dosing.

Exploratory PK Analyses

Plasma PK parameters for the riluzole metabolites N-OH-riluzole-O-glucuronide and N-OH-riluzole were similar after administration of BHV-0223, and a riluzole tablet swallowed with water (Tables S1 and S2), and ratios for $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} were within the 80% to 125% range (Table S3). Riluzolamide was assessed in plasma but was not detected. Urine PK parameters for the riluzole metabolites N-OH-riluzole, N-OH-riluzole-O-glucuronide, and riluzole

Table 4. Summary of AEs

	Fasted 40-mg Sublingual BHV-0223 (n = 137)	50-mg Oral Riluzole Tablets, Swallowed With Water (n = 138)	Fed 40-mg Sublingual BHV-0223 (n = 67)	50-mg Oral Riluzole Tablets, Crushed (n = 6)	Overall (n = 138)
Number of AEs, n (%)	157	26	63	7	253
Mild	153 (97.4)	24 (92.3)	60 (95.2)	7 (100)	244 (96.4)
Moderate	4 (2.5)	2 (7.7)	3 (4.8)	0	9
Severe	0	0	0	0	0
Number of related AEs	144 (91.7)	16 (61.5)	53 (84.1)	7 (100)	220 (87.0)
Subjects with ≥1 AE, n (%)	118 (86.1)	23 (16.7)	45 (67.2)	6 (100)	126 (91.3)
Hypoesthesia oral	111 (81.0)	0	40 (59.7)	6 (100)	116 (84.1)
Dysphagia	9 (6.6)	0	6 (9.0)	0	14 (10.1)
Headache	6 (4.4)	7 (5.1)	4 (6.0)	1 (16.7)	14 (10.1)
Discontinuations due to AEs, n	1	1	0	0	2

AE, adverse event.

glucuronide were also similar between the 2 treatments (Tables S4 and S5).

Discussion

BHV-0223 is an oral disintegrating tablet formulation of riluzole (40 mg) designed to be administered sublingually to treat patients with ALS. The results of this study demonstrate that the 40-mg BHV-0223 sublingual oral disintegrating tablet formulation was bioequivalent to the standard 50-mg riluzole tablet in the fasted state. BHV-0223 satisfied bioequivalence criteria based on the geometric LS mean ratios for AUC and C_{max}, which were approximately 90% and 113%, respectively, with 90%CIs that fell within the accepted bioequivalence criteria. In the fed state, BHV-0223 satisfied the bioequivalence criteria based on the geometric LS mean ratios for AUC_{0-t} and $AUC_{0-\infty}$, which were 91% and 92%, respectively, with 90%CIs that fell within the bioequivalence criteria. The geometric LS mean ratio for C_{max} did not meet the bioequivalence criteria under fed conditions.

While the role of AUC vs C_{max}-mediated efficacy for riluzole in ALS has not explicitly been studied, AUC exposure has been shown to drive efficacy outcomes in other neurodegenerative diseases.[23,24] Indeed, it is often advantageous to reduce C_{max} (ie, maintain overall exposure while reducing peak-to-trough ratios) with the aim to mitigate AEs that are concentration dependent. For example, patients who received riluzole tablets and had high peak levels were more likely to report diarrhea.[18] Therefore, a lower C_{max} may have the potential benefit of preventing AEs and better enable long-term adherence to therapy.

BHV-0223 was associated with reduced PK variability compared with the tablet formulation, with lower CVs on multiple exposure parameters (AUC and C_{max}). BHV-0223 exhibits predictable PK performance most likely attributable to its sublingual route of administration that mitigates variable absorption in the gastrointestinal tract and first-pass effects through the liver. A post hoc analysis demonstrated that reduced PK variability with BHV-0223 is most evident in subjects with the highest exposures. The clinical importance of this observation is based on the known benefit-risk profile of riluzole tablets, as higher levels of riluzole exposure are associated with increased safety risk without enhanced efficacy,[14] suggesting that subjects administered BHV-0223 would be less likely to achieve inappropriately high exposures, relative to the riluzole tablet.

The riluzole load for the tablet formulation is 25% greater than for BHV-0223 (50 mg vs 40 mg, respectively). BHV-0223 is predicted to confer a diminished risk of dose-related hepatotoxicity, compared with the standard, orally administered riluzole tablet formulation, since it delivers a lower overall drug burden of riluzole and bypasses first-pass metabolism in the liver.[22] The lower riluzole burden of BHV-0223 was not associated with marked liver function test (LFT) elevations (ie, ≥2 × ULN). The 100-mg riluzole daily dose (50 mg twice daily) is associated with increased rates of alanine aminotransferase ≥5 × ULN compared with placebo, whereas lower doses of riluzole, such as a 50-mg daily dose (25 mg twice daily), were not.[14] Given the increased incidence of LFT abnormalities that emerge at a 100-mg daily dose of riluzole, the lower 80-mg daily dose of riluzole delivered with BHV-0223 (40 mg) is anticipated to confer diminished risk for marked LFT elevations.

Overall, the BHV-0223 was safe and well tolerated in healthy adult subjects; no deaths or other serious AEs were reported in this study. The treatment-emergent

AEs reported in this study were consistent with riluzole tablets based on previous studies and clinical experience in patients with ALS.[14,25] Thus, the safety profile of BHV-0223 was consistent with the known safety profile of riluzole tablets.

In this study, a higher proportion of subjects treated with BHV-0223 experienced mild, transient oral hypoesthesia than subjects treated with a whole riluzole tablet. This transient phenomenon (ie, circumoral or oral numbness/paresthesia) is known to occur in people treated with riluzole[14,25] because one of the well-described pharmacological effects of riluzole is inhibition of voltage-gated sodium currents and channels.[26] This is supported by the observation that all subjects who were administered a crushed riluzole tablet also experienced oral hypoesthesia.

Fourteen subjects had mild, transient dysphagia (median duration, 34 minutes; maximum duration, 58 minutes) following administration of BHV-0223 that was concurrent with oral hypoesthesia, suggesting that the dysphagia was likely related to hypoesthesia of the oropharynx. In addition, these subjects did not report coughing, choking, or aspiration, which are common functional consequences of dysphagia, thus suggesting that the oral hypoesthesia presented a phenomenon that was perceived as dysphagia but did not affect normal swallowing function. Of note, this speculation is consistent with preliminary data from a healthy volunteer study using video fluoroscopic evaluation of swallowing after ingestion of BHV-0223, in which one subject cited difficulty swallowing but had no radiologic evidence of altered dynamics.[27] None of the patients withdrew from this study due to oral numbness and, although hypoesthesia and dysphagia were reported with BHV-0223, the local tolerability and oral safety assessments indicated no clinically important, lasting effects after a single dose of the drug.

Study limitations include the study population of healthy volunteers. It is unclear whether the AE profile of BHV-0223, particularly, oral hypoesthesia and its lack of association with swallowing difficulty, would be found in patients with preexisting dysphagia from ALS. Therefore, the AE profile of BHV-0223 would need to be assessed in an ALS patient population.

Conclusions

BHV-0223 is an oral disintegrating tablet formulation of riluzole designed to be administered sublingually to treat patients with ALS. The findings presented here show that BHV-0223 was bioequivalent to the 50-mg riluzole tablet in the fasted state in healthy adult volunteers. Food did not affect the overall systemic drug exposure of BHV-0223.

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Conflicts of Interest

I.Q., M.L., V.W., V.C., and R.M.B. are employees and shareholders of Biohaven Pharmaceuticals, Inc. M.T. and R.L. are employees of SyneosHealth (formerly known as inVentiv Health), which was the research organization contracted to conduct the present study. M.S.A. and S.H. are employees of Certara.

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Data Accessibility Statement

Access to data will be considered upon request, and inquiries should be directed to the corresponding author (robert.berman@biohavenpharma.com).

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