Riluzole Oral Suspension: Bioavailability Following Percutaneous Gastrostomy Tube-modeled Administration Versus Direct Oral Administration

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ABSTRACT

Purpose: During amyotrophic lateral sclerosis progression, up to 85% of patients develop dysphagia. Riluzole oral suspension 50 mg/10 mL is bioequivalent to riluzole 50-mg film-coated tablets administered orally under fasting conditions. Here, we compare the bioavailability of a single 50-mg dose of riluzole oral suspension via intragastric tube, a proxy for percutaneous endoscopic gastrostomy administration, with that of oral administration in healthy volunteers under fasting conditions. Secondary objectives included the plasma pharmacokinetic and safety profiles of each administration route.

Methods: This was a single-center, single-dose, open-label, randomized, 2-period, 2-sequence, crossover bioequivalence/bioavailability study. Healthy volunteers were randomized to riluzole oral suspension 50 mg/10 mL either via nasogastric tube or orally, with a 5-day washout before crossover.

Findings: A total of 32 subjects were randomized (safety population); 30 were eligible for pharmacokinetic analysis. The ratios (nasogastric tube/oral) of the geometric least squares means and the geometric 90% CIs of AUC_{0-t}, AUC_{0-inf}, and C_{max} were calculated to be 90.60% (85.66%−95.82%), 90.43% (85.47%−95.67%), and 96.99% (89.40%−105.23%), respectively, indicating bioequivalence. No significant differences in C_{max}, T_{max}, K_{el}, and $t_{1/2el}$ between treatments were found. Overall, riluzole oral suspension was well tolerated. No deaths or other serious adverse events were reported.

Implications: In this study, riluzole oral suspension was bioequivalent when administered intragastrically and orally in healthy subjects under fasting conditions. Both administration methods were well tolerated. These results show that intragastric administration of riluzole oral suspension may provide an important formulation option in people with amyotrophic lateral sclerosis who have a percutaneous endoscopic gastrostomy tube. (*Clin Ther*. 2019;41:XXX−XXX) © 2019 Elsevier Inc. (*Clin Ther*. xxxx;xxx:xxx) © 2019 Published by Elsevier Inc.

Key words: Amyotrophic lateral sclerosis, bioavailability, bioequivalence, riluzole.

INTRODUCTION

Dysphagia is one of the most critical problems affecting people with amyotrophic lateral sclerosis (ALS) and leads to increased morbidity and mortality in the >85% who develop this condition.[1−3] Dysphagia is caused by ALS progression and is related to tongue weakness and dysfunction in soft-palate and larynx closure, as well as laryngeal and diaphragmatic weakness. Symptoms include difficulty initiating swallowing; coughing or choking before, during, or after swallowing; food regurgitation; nasal regurgitation; and hoarseness and/or nasal speech.[4,5] Serious complications associated with dysphagia include choking; malnutrition, dehydration, and weight loss (negative prognostic factors in people with ALS); and aspiration pneumonia (a major cause of mortality).[1,5−8]

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In addition to deleteriously affecting nutrition intake and quality of life, the presence of dysphagia can also seriously affect the administration of beneficial medications.[3,9] Patients tend to adapt to slowly deteriorating swallowing function by changing or modifying their foods and medicines, thickening their liquids, or by prolonging meal times, often resulting in a failure to take medications as prescribed. Patients taking solid medications are challenged—often crushing tablets and/or taking medications with food to compensate—and nonadherence is common.[10,11] In particular, crushing pills and/or taking them with food may alter absorption rates or change the effective dose.[10,12] Crushing tablets may be especially salient for riluzole, because pharmacokinetics (PK) studies have shown significant decreases in C_{max} and AUC when riluzole is taken with a high-fat meal; C_{max} decreased by 44% and AUC decreased by 17.5%.[13] Furthermore, crushing riluzole disrupts the film coating of the tablet, which is designed to minimize the anesthetic effect of the drug within the mouth and throat.[12] Because larynx sensory deficit occurs in the majority of people with ALS who develop dysphagia, a potential increase in the anesthetic effect of riluzole in a patient with underlying decreased larynx sensitivity could further impair that patient's ability to swallow, and thus increase the risk for aspiration.[14]

The majority of people with ALS will eventually require enteral-nutrition support, necessitating the insertion of a percutaneous endoscopy gastrostomy (PEG) tube.[15] Challenges associated with administering solid drugs via a PEG tube are similar to those associated with oral administration in patients with dysphagia. Tablets must be crushed, potentially altering the PK properties.[12] Occlusions of the PEG tube occur in 23% to 35% of patients, and crushed tablets are a common cause.[16–18] Crushing enteric-coated tablets is especially problematic because the broken pieces will bond together when moist.[19] Occlusions may cause dehydration, malnutrition, and/or the need for additional surgery. Consequently, in patients with enteral feeding tubes, liquid formulations of medications are recommended when available.[17,18]

Riluzole oral suspension* (50 mg/10 mL) was first approved for use in the United Kingdom in 2015.[20–24] It has been established as bioequivalent to the tablet formulation under fasting conditions when taken orally.[22] This oral suspension of riluzole has not been associated with the difficulty and challenges that patients experience when taking tablets or crushing solid medications—allowing ease of administration if a patient develops dysphagia.[25] People living with ALS can continue to take riluzole throughout the course of their illness. In addition, dosing is more accurate in comparison with crushed riluzole tablets, and the facility of using an already-liquid medicine may improve compliance and adherence.

*Trademarks: Tiglutik® (Israel, Turkey, United States); Teglutik® (Australia, Austria, Belgium, France, Germany, Greece, Italy, Poland, Portugal, Spain, Switzerland, United Kingdom)[20–24] (Italfarmaco SpA, Milan, Italy).

To determine whether riluzole oral suspension administered via a PEG tube is bioequivalent to the drug administered orally, the current study compared the rate and extent of absorption of a single dose (50 mg/10 mL) via a nasogastric tube (NGT) versus oral administration in fasting, healthy adults. Administration via NGT was used as a way of modeling a PEG tube in healthy adults, because both are positioned in the stomach, are similar in composition (primarily polyurethane and silicone), and are compatible with riluzole oral suspension. Secondary objectives included comparing the plasma PK profile and the safety profile of riluzole oral suspension administered intragastrically with profiles when administered orally.

SUBJECTS AND METHODS

Study Population

Eligible volunteer subjects were healthy adult nonsmokers (no nicotine use within the 3 months before screening), 18 to 55 years of age, with no clinically significant illness or surgery within 4 weeks and no clinically significant history of neurologic, endocrinal, cardiovascular, pulmonary, hematologic, immunologic, psychiatric, gastrointestinal, renal, hepatic, or metabolic disease. The body mass index was required to be > 18.5 and < 30.0 kg/m^2, with a body weight of $\geq$50.0 kg in men and $\geq$45.0 kg in women. During the study, subjects took no concurrent medications, including over-the-counter products, natural health products, and homeopathic or herbal remedies, with the exception of oral contraceptives and limited acetaminophen use.

Women of childbearing potential were to use an acceptable contraceptive method throughout the study and for 30 days after the last study drug administration.

Exclusion criteria included any abnormality of the nose/nostrils that would prevent an adequate NGT insertion or any clinically significant abnormality at physical examination or abnormal laboratory test result, ECG abnormality, or vital sign abnormality at screening. Subjects were excluded if found to have a positive result for hepatitis B virus, hepatitis C virus, or HIV during medical screening; gastrointestinal disease within 3 months prior to, or at, dosing; any nasal surgery within 3 months prior to dosing; positive urine drug screen or urine cotinine test at screening; history of allergic reactions to riluzole or other related drugs; use of any drugs known to induce or inhibit hepatic cytochrome P450 1A2 metabolism within 30 days prior to the first study drug administration; positive pregnancy test at screening; or if they were breastfeeding. Subjects could not have a history of significant alcohol abuse within 1 year prior to screening or regular use of alcohol within 6 months prior to the screening visit. Subjects could not have a history of significant drug abuse within 1 year prior to screening, use of soft drugs within 3 months prior to the screening visit, or use of hard drugs within 1 year prior to screening. Subjects could not have: participated in a clinical research study involving the administration of an investigational or marketed drug or device within 30 days prior to the first dosing, participated in a clinical research study involving the administration of a biological product within 90 days prior to the first dosing, or concurrent participation in an investigational study regardless of whether a drug or device is administered.

The PK population was composed of all subjects who completed the study without a major protocol violation and in whom the PK profile could be adequately characterized. Data from subjects who withdrew due to an adverse event (AE) or who had a predose concentration greater than C_{max} were excluded from the descriptive statistics.

Study Design

This study was conducted between April 30, 2017, and June 12, 2017, at a single site in Canada (inVentiv Health Clinique Inc, Quebec City, Quebec, Canada). The clinical study protocol, any relevant associated documents, and informed-consent forms were reviewed and approved by an independent ethics committee (IRB Services, Ontario, Canada) prior to beginning associated study procedures. All clinical work was conducted in compliance with the Good Clinical Practice guideline as referenced in the International Conference on Harmonisation guideline (ICH E6), Good Laboratory Practices as referenced in the International Conference on Harmonisation guideline, local regulatory requirements, and the recommendations laid down in the most recent version of the Declaration of Helsinki. All subjects were provided with an informed consent form in their language of preference (either French or English) for review.

In this open-label study, subjects were initially randomized to 1 of 2 treatment arms: riluzole oral suspension (50 mg/10 mL; supplied by Aphena Pharma Solutions, Whippany, NJ) delivered either orally or by NGT. Following a minimum-5-day washout period, subjects were crossed over to the other treatment arm. In each treatment period, subjects were confined from 10 h prior to drug administration until 24 h following administration. Subjects were fasted for at least 10 h prior to, and 4 h after, drug administration.

PEG Model

The NGT was chosen to model the intragastric administration of medication in patients with PEG. Proper placement of the NGT was evaluated by auscultation of a rush of air over the stomach using the 60-mL feeding syringe and/or by the aspiration of gastric content. Although PEG and NGT are different in terms of length (which may affect drug flow in the tubes), riluzole oral suspension was flushed from the NGT with 30 mL of water before and after the administration of riluzole oral suspension, as described by the guideline on enteral feeding.[26] The subjects subsequently drank 170 mL of water. In the oral administration, subjects drank riluzole oral suspension (50 mg/10 mL) from a glass. Afterward, the glass was rinsed twice with 115 mL of water, which the subject drank, for a total of 230 mL.

Pharmacokinetic Assessments

Blood samples of 3 mL each were collected at 17 time intervals during each 24-h monitoring period.

All blood samples were collected in labeled K_2EDTA tubes by dead-volume IV catheter or by direct venipuncture. Blood samples were cooled in an ice/water bath and were centrifuged (within 230 min of collection) at 2000*g* ± 5*g* at approximately 4 °C for at least 10 min. Aliquots of plasma were then pipetted into polypropylene tubes for freezing and storage at −80 °C until analysis.

At the end of the study, all samples were transferred to the bioanalytical facility (inVentiv) for the analysis of plasma riluzole using validated methods. After automated protein precipitation, riluzole concentrations in human plasma K_2EDTA were determined using an HPLC-MS/MS method (API 5000; column: Zorbax SB-C18, 50 × 4.6 mm, 3.5 μm; Agilent Technologies, Santa Clara, CA; mobile phase A: milli-Q type water/methanol with ammonium formate and formic acid; mobile phase B: methanol/acetonitrile with formic acid). The assay concentration range was 0.5 to 500 ng/mL using HPLC-MS/MS with automated extraction. Standard curve and quality-control samples were generated using riluzole $^{13}C,^{15}N_2$ (TLC PharmaChem Inc, Concord, Vaughan, Ontario, Canada) as an internal standard to monitor assay performance. For precision, the within-assay results showed that the % CV was 0.82% to 7.15%; the corresponding within-assay accuracies, expressed as percent bias, were −3.58% to 6.00%.

Pharmacokinetic analyses were performed using Phoenix WinNonlin version 6.4 and were based on the actual times that the samples were taken. The following PK parameters were calculated: AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, $t_{1/2el}$, K_{el}, and residual area ($1 - AUC_{0-t}/AUC_{0-inf}$). The primary PK end point was the bioequivalence assessment for NGT and oral administration, as described in the Statistical Analysis section.

Tolerability Assessments

The safety population included all subjects who received at least 1 dose of study medication. The

Table I. Demographic characteristics of the safety and pharmacokinetics (PK) populations.

Category	Safety Population (N = 32)	PK Population (N = 30)
Age, mean (SD), y	37.3 (11.0)	36.8 (11.0)
Age group, no. (%)		
18−40 y	18 (56.3)	17 (56.7)
>40 y	14 (43.8)	13 (43.3)
Sex, no. (%)		
Female	17 (53.1)	16 (53.3)
Male	15 (46.9)	14 (46.7)
Ethnicity, no. (%)		
Not Hispanic or Latino	27 (84.4)	25 (83.3)
Hispanic or Latino	5 (15.6)	5 (16.7)
Race, no. (%)		
White	29 (90.6)	28 (93.3)
Black	3 (9.4)	2 (6.7)
Height, mean (SD), cm	169.28 (7.84)	169.26 (8.11)
Weight, mean (SD), kg	73.33 (10.75)	73.39 (11.09)
BMI, mean (SD), kg/m^2	25.513 (2.630)	25.531 (2.708)

BMI = body mass index.

main tolerability measure was the record of all AEs and treatment-emergent AEs (TEAEs) that first occurred or worsened following treatment. Clinical laboratory values and vital signs were also collected at screening and study exit.

Statistical Analysis

ANOVA was performed on nontransformed T_{max}, $t_{1/2el}$, and K_{el}, and on ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} at the α level of 0.05, using general linear model procedures in SAS 9.2 or higher (SAS Institute, Cary, North Carolina). If the Treatment*Group interaction term was not statistically significant, the analysis was rerun excluding this term from the ANOVA model in order to obtain ratios and CIs, where appropriate. Bioequivalence was defined by 90% CIs for the ratio of geometric means (NGT/Oral) falling within the range of 80.00% and 125.00%, using the least squares mean values from the ANOVA of the ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max} values.[27] Intrasubject %CV calculations indicated that the study should have a power of at least 90% to show comparable extent of absorption, with 30 subjects completely evaluable. In order to account for possible dropouts, 36 subjects were intended to be included in the study.

RESULTS

Demographic Characteristics

Sixty-nine subjects were screened, and 35 were enrolled. Of these, 32 subjects received at least 1 dose of riluzole oral suspension, composing the safety population. The PK population included the 30 subjects (93.8%) who completed all treatment periods with sufficient data for PK analysis. The demographic characteristics of the safety and PK populations are shown in Table I.

Primary End Point: Bioavailability of Enteral and Oral Administrations

The primary end point of this study was to determine bioequivalence of the oral and enteral routes of administering riluzole oral suspension. The residual area was <20% with both treatments, indicating sufficient sampling duration (mean [SD]: NGT, 7.79% [2.90]; oral, 7.78% [3.30]). Statistical analysis found that NGT and oral administrations were bioequivalent: The ratios (NGT/Oral) of the geometric least squares means and the lower and upper limits of the geometric 90% CIs of AUC0−t, AUC0−inf, and Cmax were calculated to be 90.60% (85.66%−95.82%), 90.43% (85.47%−95.67%), and 96.99% (89.40%−105.23%), respectively, indicating bioequivalence, as the 90% CIs for the ratio of geometric means (NGT/Oral) based on the least squares means of AUC_{0-t}, AUC_{0-inf}, and C_{max} were within the 80.00% to 125.00% window (Table II).

Secondary Pharmacokinetic End Points

The results for AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, $t_{1/2el}$, and K_{el} under fasting conditions are shown in Table III. Both AUC_{0-t} and AUC_{0-inf} were significantly greater with oral administration than via NGT (both, $P < 0.05$). No significant between-group differences in C_{max}, T_{max}, $t_{1/2el}$, or K_{el} were found. The differences in plasma concentration−time with the NGT and oral administrations are shown in the Figure.

Table II. Ratios of pharmacokinetic (PK) parameters (NGT group/Oral group), with ratios of the least squares means of the ln-transformed values.

Parameter	Treatment Comparison	Least Squares Means (NGT, Oral)	Ratio, %*	Geometric 90% CI†
AUC_{0-t}	NGT−Oral	6.159334, 6.258093	90.06	85.66−95.82
AUC_{0-inf}	NGT−Oral	6.239882, 6.340480	90.43	85.47−95.67
C_{max}	NGT−Oral	4.961273, 4.991806	96.99	89.40−105.23

NGT = nasogastric tube.
* Calculated using least squares means according to the formula $e^{(Difference)} \times 100$.
† Geometric 90% CI using ln-transformed data.

Table III. Summary of PK properties for riluzole oral suspension (PK population; N = 30). Data are given as mean (SD) unless otherwise specified.

Parameter	Riluzole 50-mg Oral Suspension NGT		Riluzole 50-mg Oral Suspension Orally	
	Mean (SD)	%CV	Mean (SD)	%CV
AUC_{0-t}, h · ng/mL	512.36 (213.58)	41.69	574.24 (258.86)	45.08
AUC_{0-inf}, h · ng/mL	558.84 (240.58)	43.05	627.61 (294.45)	46.92
Residual area, %	7.79 (2.90)	37.28	7.78 (3.30)	42.36
C_{max}, ng/mL	159.55 (79.24)	49.67	163.12 (75.41)	46.23
T_{max}, h*	0.745 (0.494–0.999)	–	0.745 (0.494–1.013)	–
$t_{1/2el}$, h	7.63 (1.24)	16.24	7.52 (1.45)	19.31
K_{el}, per h	0.0930 (0.0139)	14.9473	0.0949 (0.0153)	16.1508
Correlation	–0.9804 (0.0128)	nc	–0.9824 (0.0110)	nc
$K_{el\ Lower}$, h	5.998 (0.005)	0.077	5.998 (0.004)	0.061
$K_{el\ Upper}$, h	24.007 (0.016)	0.67	24.013 (0.030)	0.123

nc = not calculated; NGT = nasogastric tube.
* Median (range).

Tolerability Analysis

There were 47 TEAEs reported by 24 of the 32 subjects in the safety population. About twice as many TEAEs were reported with oral administration (31 events in 20 subjects [62.5%]) as with NGT administration (16 events in 9 subjects [29.0%]). No serious or severe TEAEs were reported, and there were no discontinuations due to AEs. Almost all TEAEs were mild and resolved by the end of the study (Table IV). The most common TEAE was oral hypoesthesia, which occurred in 50.0% of subjects but only with the oral administration. All cases were of mild severity and resolved spontaneously by the end of the study. There were no clinically relevant changes in clinical laboratory parameters or vital signs.

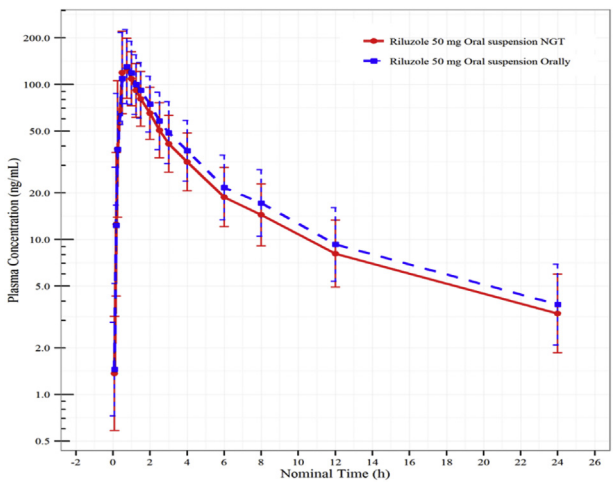

Figure. Mean (SD) concentration–time profile of riluzole oral suspension (50 mg/10 mL), by route of administration. Logarithmic scale.

DISCUSSION

The results of this study indicate that riluzole oral suspension (50 mg/10 mL) has a rate of absorption over time that was similar between administration by a PEG-modeled system and oral administration. For AUC_{0-t}, AUC_{0-inf}, and C_{max}, the 90% CIs of the ratios of geometric means (NGT/Oral) based on least squares means were all within the 80.00% to 125.00% window, indicating bioequivalence between the intragastric and oral delivery methods. Small but statistically significant between-group differences in AUC_{0-t} and AUC_{0-inf} were found with oral versus enteral administration of riluzole oral suspension.

Table IV. Summary of adverse events.

Parameter	Riluzole 50-mg Oral Suspension NGT (n = 31)	Riluzole 50-mg Oral Suspension Orally (n = 32)	Overall (N = 32)
Subjects with at least 1 TEAE, no. (%)	9 (29.0)	20 (62.5)	24 (75.0)
Total TEAEs	16	31	47
Treatment-related	8	21	29
Hypoesthesia oral, no. (%)	0	16 (50.0)	16 (50.0)
Abdominal pain, no. (%)	1 (3.2)	0	1 (3.1)
Nausea, no. (%)	0	1 (3.1)	1 (3.1)
Vomiting, no. (%)	0	1 (3.1)	1 (3.1)
Somnolence, no. (%)	3 (9.7)	0	3 (9.4)
Headache, no. (%)	3 (9.7)	0	3 (9.4)
Dizziness, no. (%)	0	1 (3.1)	1 (3.1)
Cough, no. (%)	0	1 (3.1)	1 (3.1)
Chills, no. (%)	1 (3.2)	0	1 (3.1)
Asymptomatic bacteriuria, no. (%)	0	1 (3.1)	1 (3.1)
Severe, no.	0	0	0
Serious, no.	0	0	0
Discontinuations due to TEAEs, no.	0	0	0
Deaths, no.	0	0	0

NGT = nasogastric tube; TEAE = treatment-emergent adverse event.

These differences were probably due to the slight delay in time of absorption with oral administration and were unlikely to have been clinically meaningful. No significant differences in any other PK parameters measured were found.

The tolerability data support the results from previous clinical trials demonstrating that riluzole oral suspension (50 mg/10 mL) is generally well tolerated when administered orally and indicate that there were no new, emerging AEs with intragastric administration.[21,22] There were no discontinuations and no severe or serious TEAEs, and most TEAEs resolved by study exit.

The most common TEAE was oral hypoesthesia, which was observed only when riluzole suspension was administered orally. Riluzole has intrinsic anesthetic properties due to partial blocking of sodium channels.[28,29] The patient dosing instructions on riluzole oral suspension indicate that it should be administered by syringe, either along the inside of the cheek or on the center of the tongue to help reduce the anesthetic effect.[30,31] Unlike the dosing instructions in the prescribing information, the methodology in this study required that subjects drink riluzole oral suspension from a glass. Administering riluzole oral suspension as liquid bathing the tongue may have increased the rate of oral hypoesthesia that was observed in this study.

Dysphagia is a common consequence of ALS. It is present in about half of patients with ALS at onset, and up to 85% will develop this condition.[3] It has also been associated with serious negative outcomes, including malnutrition and weight loss, dehydration, and pulmonary aspiration.[5,7]

Dysphagia presents a particular challenge with medications available in tablet formulation. The inability of a patient to swallow a tablet may result in poor treatment adherence and early discontinuation of a necessary treatment. By changing or modifying medications, such as crushing riluzole—which is routinely done[3]—dosage errors may result from incomplete delivery of medicine, or alterations in the tolerability and efficacy of

medications may ensue.[10–12,32] The recent introduction of riluzole oral suspension (50 mg/10 mL), which has been shown to be bioequivalent to the 50-mg tablet formulation,[22] fills an important unmet medical need in people with ALS who have co-occurrence of dysphagia.

The majority of people with ALS will eventually require the insertion of a PEG tube.[15] Clinical guidelines recommend PEG in people with ALS who are not getting proper nutrition or who are showing weight loss. PEG has been associated with increased survival in people with ALS.[33,34] It is also associated with improved quality of life in ~85% of patients who receive it, with no patients reporting worsened quality of life.[9] Clinical guidelines recommend early tube placement so that patients can benefit from nutritional support before malnutrition, weight loss, and dehydration have further progressed, and before patients are no longer candidates for the surgery to implant a PEG tube.[35,36]

PEG tubes, despite their potential clinical benefits, pose significant challenges for medication administration. Crushing riluzole tablets for the purpose of administration via a PEG tube falls outside of the scope of the prescribing instructions. Administering crushed tablets via an enteral feeding tube introduces the potential for tube blockage, incorrect or incomplete dosing, and poor cleanliness and infection control.[12,19] These issues have not been associated with liquid formulations.[12,19] The current PK study found that, in healthy adult subjects under fasting conditions, riluzole oral suspension administered intragastrically via a PEG-modeled system is bioequivalent to riluzole oral suspension administered orally, with similar tolerability.

CONCLUSIONS

Riluzole is a disease-modifying treatment that has been shown to slow the course of ALS. Based on the bioequivalence of oral and intragastric administration, this study demonstrates that riluzole oral suspension provides an important formulation option for people with ALS who have a PEG tube.

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B.R. Brooks contributed to the conceptualization, methodology, formal analysis, validation, and visualization of the study. P. Bettica and S. Cazzaniga contributed to the methodology and supervision of the study. S. Cazzaniga contributed to project administration. All of the authors contributed equally to the article and approved the final version for submission.

CONFLICTS OF INTEREST

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