NCT03679975

A Single Center Study to Evaluate the Effect of Riluzole Oral Soluble Film on Swallowing Safety in Individuals With Amyotrophic Lateral Sclerosis

Protocol
18-Oct-2017

A Single Center Study to Evaluate the Effect of Riluzole Oral Soluble Film on Swallowing Safety in Individuals With Amyotrophic Lateral Sclerosis

Amendment 1
Summary of Changes from Version 1.0 (July 27, 2017) to Version 2.0 (October 18, 2017)

Note:

Major changes described in the following table have been made in this document to address the following issues:

- **Additional exclusion added to clarify the exclusion for the PAS score applies to any previous swallowing studies**
- **Additional exclusion added for subjects with a history of two or more episodes of aspiration pneumonia requiring hospitalization**
- **Modified hepatic function exclusion requirement for subjects currently on Riluzole**
- **Modified hepatic function exclusion requirement for subjects receiving Riluzole for the first time**
- **Added description of comprehensive and brief physical examinations and comprehensive neurological and brief neurological examinations**

Few minor changes involving wordsmithing for clarity and consistency, punctuation, and correction of typos have also been made but are not included in this table because they are not substantive changes. However, they are visible in the tracked-changes version of the protocol

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Section	Version No 1.0 July 27, 2017	Amendment 1 (Version 2.0) October 18, 2017	Rationale
3. Synopsis – Exclusion Criteria		*p 7* 2. Subjects with a prior swallowing study that has shown a PAS of 3 or greater 3. Subjects with a history of two or more episodes of aspiration pneumonia requiring hospitalization	Additional exclusions added in response to Information Request (IR) - IND 130939-Comments on new protocol submission/SN0003_24_August_2017
3. Synopsis – Exclusion Criteria	*p 7* ~~*8. Subjects with hepatic impairment as defined by baseline elevations of serum aminotransferases greater than 5 times upper limit of normal or evidence of liver dysfunction (e.g., elevated bilirubin).*~~	*p 7* *10.* Subjects currently taking riluzole with ALT levels greater than 5 times upper limit of normal or with evidence of clinical jaundice. (Riluzole should be discontinued in these patients).	Changed to be consistent with the Reference Listed Drug (RLD), RILUTEK (NDA 020599) label
3. Synopsis – Exclusion Criteria		*P 7* *11.* Subjects who will be receiving riluzole for the first time who exhibit baseline elevations of several LFTs (especially elevated bilirubin). (These findings at baseline should preclude the use of riluzole including ROSF.).	Added to be consistent with the Reference Listed Drug (RLD), RILUTEK (NDA 020599) label
8.1.2 Exclusion		*p 18* 2. Subjects with a prior	Additional exclusions added in response to Information Request (IR) - IND

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Section	Version No 1.0 July 27, 2017	Amendment 1 (Version 2.0) October 18, 2017	Rationale
Criteria		swallowing study that has shown a PAS of 3 or greater 3. Subjects with a history of two or more episodes of aspiration pneumonia requiring hospitalization	130939-Comments on new protocol submission/SN0003_24_August_2017
8.1.2 Exclusion Criteria	*P 19* *8. ~~Subjects with hepatic impairment as defined by baseline elevations of serum aminotransferases greater than 5 times upper limit of normal or evidence of liver dysfunction (e.g., elevated bilirubin).~~*	*P 19* *10..* Subjects currently taking riluzole with ALT levels greater than 5 times upper limit of normal or with evidence of clinical jaundice. (Riluzole should be discontinued in these patients .)	Changed to be consistent with the Reference Listed Drug (RLD), RILUTEK (NDA 020599) label
8.1.2 Exclusion Criteria		*P 19* 11. Subjects who will be receiving riluzole for the first time who exhibit baseline elevations of several LFTs (especially elevated bilirubin). (These findings at baseline should preclude the use of riluzole including ROSF.).	Added to be consistent with the Reference Listed Drug (RLD), RILUTEK (NDA 020599) label
10.2.2.1. Videofluoroscopy Swallow Study (VFSS 1-PAS)		*P 27* The start time and finish time for the standardized bolus protocol will be recorded for both VFSS 1 and VFSS 2.	Added in response to Information Request (IR) - IND 130939-Comments on new protocol submission/SN0003_24_August_2017

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Section	Version No 1.0 July 27, 2017	Amendment 1 (Version 2.0) October 18, 2017	Rationale
10.2.2.1. Videofluoroscopy Swallow Study (VFSS 1-PAS)	*P 26* *Immediately following VFSS 1-PAS, the patient will then be administered ROSF on the dorsum of tongue along the median lingual sulcus.*	*P 28* *...sulcus, ,* and the time of administration will be recorded.	Added in response to Information Request (IR) - IND 130939-Comments on new protocol submission/SN0003_24_August_2017
10.2.2.1. Videofluoroscopy Swallow Study (VFSS 1-PAS)		*P 28* The investigator should record whether or not ROSF is fully dissolved at 3 minutes after dosing. In the event that ROSF is not fully dissolved at 3 minutes, the investigator will record the time that it is confirmed that ROSF is fully dissolved.	Added in response to Information Request (IR) - IND 130939-Comments on new protocol submission/SN0003_24_August_2017
10.3.6. Clinical Assessments		*P 30* Subjects will undergo a comprehensive physical and neurological examination at screening, and a brief physical and neurological examination at Visit 1 following the second VFSS. The comprehensive physical examination will include complete vital signs, weight, height, general appearance, and evaluation of systems: head, ears, eyes, nose, and throat; respiratory; abdomen; lymph nodes; spine; skin; cardiovascular; and	The CRO managing the protocol requested a description of the comprehensive and the brief physical exam and the neurological exam and brief neurological exam

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Section	Version No 1.0 July 27, 2017	Amendment 1 (Version 2.0) October 18, 2017	Rationale
		extremities. The brief general physical examination will include abbreviated vital signs (blood pressure, heart rate, respiratory rate), and examination of the cardiovascular and respiratory systems and abdomen. Other elements may be included depending on symptoms or physical findings. The comprehensive neurological examination will include (as permitted by the patient's capabilities) cranial nerves 2-12, muscle tone and strength, tendon reflexes and plantar response, sensory function (pain, light touch, position, vibration), coordination (finger-nose), and gait. The brief neurological examination will include cranial nerves 2-12, muscle strength, tendon reflexes, plantar response, and sensory function (pain, light touch, position, vibration). Other elements may be included depending on symptoms or physical findings	
10.3.12. Physical and Neurological Examinatio		*P 34* Subjects will undergo a comprehensive physical and neurological examination at screening, and a brief physical	The CRO managing the protocol requested a description of the comprehensive and the brief physical exam and the neurological exam and brief

Section	Version No 1.0 July 27, 2017	Amendment 1 (Version 2.0) October 18, 2017	Rationale
n		and neurological examination at Visit 1 following the second VFSS. The comprehensive physical examination will include complete vital signs, weight, height, general appearance, and evaluation of systems: head, ears, eyes, nose, and throat; respiratory; abdomen; lymph nodes; spine; skin; cardiovascular; and extremities. The brief general physical examination will include abbreviated vital signs (blood pressure, heart rate, respiratory rate), and examination of the cardiovascular and respiratory systems and abdomen. Other elements may be included depending on symptoms or physical findings. The comprehensive neurological examination will include (as permitted by the patient's capabilities) cranial nerves 2-12, muscle tone and strength, tendon reflexes and plantar response, sensory function (pain, light touch, position, vibration), coordination (finger-nose), and gait. The brief neurological examination will include cranial nerves 2-12, muscle strength, tendon reflexes, plantar response, and	neurological exam

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		sensory function (pain, light touch, position, vibration). Other elements may be included depending on symptoms or physical findings.	

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FULL STUDY TITLE

A Single Center Study to Evaluate the Effect of Riluzole Oral Soluble Film on Swallowing Safety in Individuals With Amyotrophic Lateral Sclerosis

SHORT STUDY TITLE

Riluzole Oral Soluble Film Swallowing Safety in Amyotrophic Lateral Sclerosis

Protocol Number: 17MO1R-0012

Protocol Version Number: Amendment 1, V2.0
Protocol Version Date: October 18, 2017

Sponsor:
MonoSol Rx, LLC
30 Technology Drive
Warren, NJ 07059
USA

Phase 2

IND Number: 130939

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The information contained herein is confidential and proprietary in nature, and will not be disclosed to any third party without written approval of authorized designee. This document may be disclosed to the appropriate institutional review boards or to duly authorized representatives of the US Food and Drug Administration or a national regulatory authority under the condition that they maintain confidentiality.

1. PROTOCOL APPROVAL SIGNATORY PAGE

Study Title: A Single Center Study to Evaluate the Effect of Riluzole Oral Soluble Film on Swallowing Safety in Individuals With Amyotrophic Lateral Sclerosis

SAFETY APPROVAL

I have read this protocol and agree that the design of the protocol adequately protects the safety of the patients.

Allen H. Heller — 23 Oct 2017

Allen H Heller MD MPH, Date:
Principal, Pharma Study Design, LLC

(Consultant to MonoSol Rx)

SPONSOR APPROVAL

I have read this protocol and agree that the sponsor will use appropriate control processes to ensure that the sponsor's activities meet the requirements of applicable regulatory agencies:

10/23/17

Dan Barber, VP, Value Creation Date
MonoSolRx, LLC

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2. INVESTIGATORS AND FACILITIES

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3. SYNOPSIS

Title	A single center study to evaluate the effect of Riluzole Oral Soluble Film (ROSF) on swallowing safety in individuals with amyotrophic lateral sclerosis.
Objectives	The primary objective is to evaluate the effect, if any, of a single 50 mg dose of Riluzole Oral Soluble Film (ROSF) on swallowing safety in individuals with amyotrophic lateral sclerosis.
Experimental Design	This is a single site, single dose, open-label safety study. Approximately thirty (30) individuals with amyotrophic lateral sclerosis (ALS) will be enrolled. Subjects seen in the ALS Clinic at the University of Florida will be screened to determine eligibility according to the specified inclusion/exclusion criteria. Following enrollment and informed consent, subjects will undergo a clinical evaluation including the validated Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R). Swallowing safety will be assessed using the gold standard Videofluoroscopic Swallowing Study to afford direct visualization of the swallowing process and any episodes of penetration or aspiration quantified using the validated Penetration Aspiration Scale (PAS). Subjects will undergo a standardized protocol that includes 12 bolus stimuli presentations of different liquid and food materials to test the swallow across a continuum of textures and materials. Immediately following, subjects will be given a single dose of riluzole oral soluble film (ROSF) 50mg, placed on the median lingual sulcus of the dorsum of the tongue. Three minutes after the administration of ROSF, the identical standardized VFSS protocol will be re-administered to allow a comparison of swallowing safety (using the PAS scale) pre vs. post ROSF administration.
Interventions	ROSF is a new formulation of riluzole 50mg that allows for rapid dissolution of the medication through a soluble film placed on the dorsum of the tongue along the median lingual sulcus.
Study Duration Participant Duration:	The anticipated time from study enrollment until completion of data analyses is approximately 9 months. Total study participant time is expected to be approximately 30 days from time of screening to completion of study.

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Study Population and Sample Size	Approximately 30 subjects with ALS will be enrolled. The inclusion criteria are intended to provide a representative cohort of subjects with ALS who are currently on an oral diet and able to take foods and liquids by mouth, equivalent to a score of 3 or above on the Functional Oral Intake Scale (Crary, 2005). Inclusion will require a diagnosis of probable or definite ALS in accordance with the Revisited El-Escorial Criteria (Cedarbaum, 1999), a prescription to take riluzole at or before the time of the administration of study drug, no allergies or contraindications to barium, riluzole or inactive ingredients* in ROSF, and no contraindications to study procedures. Female subjects must not be pregnant or breast-feeding. *See Investigator's Brochure
Phase	2
Test Drug	Riluzole Oral Soluble Film 50 mg (MonoSol Rx, LLC)
Inclusion Criteria	1. Male or female subjects between 18-80 years of age, inclusive 2. Subjects have a diagnosis of probable or definite ALS in accordance with the Revisited El-Escorial Criteria (Cedarbaum, 1999) 3. Subjects must be currently on an oral diet and able to take foods and liquids by mouth equivalent to a score of 3 or above on the Functional Oral Intake Scale (Crary, 2005). 4. Subjects must have no known allergy to barium sulfate, riluzole or inactive ingredients* in ROSF. 5. Subjects or subject's legally authorized representative must be willing and able to complete informed consent/assent and HIPAA authorization. 6. Ability to comprehend and be informed of the nature of the study, as assessed by the PI or Sub-Investigator. 7. Subjects prescribed to take riluzole at or before the time of first dosing. (The study is open to subjects currently taking riluzole at screening, subjects who are not currently taking riluzole at screening who have taken riluzole in the past, and subjects to be newly started on riluzole (given as ROSF in the course of

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	this study). 8. Availability to volunteer for the entire study duration and willing to adhere to all protocol requirements 9. Female subjects of childbearing potential must have a negative urine pregnancy test at Screening and Visit 1. Female subjects of childbearing potential (i.e. not surgically sterile, not 2 years postmenopausal, or not with a sterile partner) must have a negative pregnancy test at screening and Visit 1, agree to abstinence, practicing double barrier contraception or using an FDA approved barrier method contraceptive (e.g., licensed hormonal or barrier methods) for greater than 2 months prior to screening visit and commit to an acceptable form of birth control for the duration of the study and for 30 days after participation in the study. *See Investigator Brochure
Exclusion Criteria	1. Subjects who score 2 or below on the Functional Oral Intake Scale (Crary, 2005) 2. Subjects with a prior swallowing study that has shown a PAS of 3 or greater 3. Subjects with a history of two or more episodes of aspiration pneumonia requiring hospitalization 4. Subjects with a history of clinically significant liver disease, renal disease, or any other medical condition judged to be exclusionary by the investigator 5. Subjects who are unwilling to sign informed consent or subjects who for any other reason in the judgment of investigator are unable to complete the study 6. Female subjects who have a positive urine pregnancy test (βhCG) at screening or visit 1, are trying to become pregnant or are breastfeeding. 7. Subjects with active cancer within the previous 2 years, except treated basal cell carcinoma of the skin 8. Subjects who have taken any experimental drug within 30 days prior to enrollment or within 5 half-lives of the investigational drug –whichever is the longer period.

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	However, subjects who have previously completed other MonoSol Rx sponsored ROSF clinical studies within the last 30 days prior to enrollment may be eligible for consideration for entry into this study. 9. Subjects with known history or presence of moderate or severe renal impairment as defined by a calculated creatinine clearance of ≤50 mL/minute 10. Subjects currently taking riluzole with ALT levels greater than 5 times upper limit of normal or with evidence of clinical jaundice. (Riluzole should be discontinued in these patients.) 11. Subjects who will be receiving riluzole for the first time who exhibit baseline elevations of several LFTs (especially elevated bilirubin). (These findings at baseline should preclude the use of Riluzole including ROSF). 12. Use of potentially hepatotoxic drugs: (e.g., allopurinol, methyldopa, sulfasalazine). 13. Subjects with clinically significant abnormal laboratory values in the judgment of the investigator 14. Use of strong or moderate CYP1A2 inhibitors (e.g., ciprofloxacin, enoxacin, fluvoxamine, methoxsalen, mexiletine, thiabendazole, vemurafenib, zileuton) and CYP1A2 inducers (e.g. rifampin and barbiturates) in the previous 30 days before drug administration. 15. Anything else that, in the opinion of the investigator, would place the subject at increased risk or preclude the subject's full compliance with or completion of the study 16. Employee or immediate relative of an employee of the investigator, MonoSol Rx LLC, any of its affiliates or partners, or inVentiv Health.

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Assessments	• Comprehensive/brief physical exam • Comprehensive/brief neurologic exam • ALS Functional Rating Scale – Revised (ALSFRS-R scale) • Functional Oral Intake Scale (Crary, 2005). • Eating Assessment Tool -10 (Belafsky, 2008) • Videofluoroscopic swallowing study (VFSS) • Penetration Aspiration Scale (PAS) (Rosenbek, 1999) • Adverse events • Clinical laboratory evaluation(s) • Urine Pregnancy Test (females of childbearing potential) • Vital Signs, Height and Weight • Medical history • Concomitant medication • Inclusion/exclusion criteria

Statistical Analysis

Primary Outcome:
The primary objective is to assess the effect of the ROSF formulation, if any, on swallowing safety in subjects with ALS. The null hypothesis is that there will be no difference between the PAS scores (i.e. swallowing safety) obtained before and after administration of the study medication.

The PAS scores obtained in swallow tests during VFSS 1-PAS (before ROSF) and VFSS 2-PAS (after ROSF) will be compared within each subject with the non-parametric Wilcoxon Signed-Rank Test. Alpha will be set at 0.05, two-tailed. Analysis across each swallowing trial will be performed, providing 12 bolus stimuli trials and approximately 35 swallows and PAS scores for each elicited swallow across testing within each participant (across various textures and swallowing complexities given that multiple swallows are typically elicited per bolus stimuli trial) to ensure a comprehensive exam across a variety of liquid volumes, textures and consistencies).

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Sample size was determined for a within-person design (repeated measures, same subjects in VFSS 1-PAS and VFSS 2-PAS) using G*Power Version 3.1.9.2, assuming a correlation = 0.6 across the two measurements. A sample size of n=25 would be able to detect at least a 1.0 point difference (two-tailed), effect size 0.6, in PAS scores from Test 1 and Test 2 with 80% power. It is anticipated that approximately 20% of recruited ALS subjects will grossly aspirate during VFSS 1-PAS and will not have a VFSS 2-PAS performed (for both safety reasons and also because Test 2 would not yield any useful data due to a ceiling effect). Therefore enrollment is planned for a total of 30 subjects to account for this potential.

Depending on the study enrollment rate, the Sponsor may elect to perform an interim analysis using available data from the subset of subjects who have completed the study at that time. The results of this interim analysis will be used only for internal planning and possibly for sharing with regulatory authorities. The results of the interim analysis will have absolutely no influence on the subsequent conduct of the study.

The following safety information will be included as descriptive summaries:

- Type, incidence, and severity of adverse events
- Physical and neurological examinations
- Vital signs (heart rate, blood pressure, rate, temperature), Height/Weight
- Clinical laboratory evaluation(s); see Section 10.3.7 *Laboratory Evaluations*
- Urine pregnancy test (females of childbearing potential)
- ALS Functional Rating Scale – Revised (ALSFRS-R) (Cedarbaum, 1999)
- Functional Oral Intake Scale – FOIS (Crary, 2005)
- Eating Assessment Tool 10 – (EAT-10) (Belafsky, 2008)

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4. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALS	amyotrophic lateral sclerosis
ALSFRS-R	ALS Functional Rating Scale-Revised
CDE	Common Data Elements
CFR	Code of Federal Regulations
CMSU	Clinical Materials Services Unit
CRF	case report form
CS	clinically significant
DM	data management
EAT-10	Eating Assessment Tool -10
EDC	electronic data capture
FDA	Food and Drug Administration
FOIS	Functional Oral Intake Scale
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council on Harmonization
MedDRA	Medical Dictionary for Regulatory Activities
NINDS	National Institute of Neurological Disorders and Stroke
PAS	Penetration Aspiration Scale
ROSF	Riluzole Oral Soluble Film
SAE	serious adverse event
SOA	schedule of activities
VFSS	Videofluoroscopic Swallowing Study

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5. TABLE OF CONTENTS

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6. BACKGROUND AND PHARMACOKINETICS

Riluzole Oral Soluble Film (ROSF) is being developed by MonoSol Rx as an alternative dosage form with an alternate route of administration for the existing FDA-approved riluzole product, Rilutek® tablets. The ROSF product contains the active ingredient riluzole incorporated into a polymer-based film matrix utilizing MonoSol Rx's PharmFilm® technology. The inactive ingredient composition, the film dimensions, and the manufacturing process selected for this drug product are based on the information gained from the development of ROSF and other film products produced by MonoSol Rx (ZUPLENZ® 4 mg and 8 mg and SUBOXONE® 2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg, and 12 mg/3 mg).

6.1. Rationale

The proposed indication for ROSF is the treatment of patients with Amyotrophic Lateral Sclerosis (ALS), the same as for Rilutek® (riluzole) tablets (US Package Insert; revision 04/2016). Clinical trials with Rilutek® tablets have shown that the time to tracheostomy or death was longer for ALS patients receiving Rilutek® compared to placebo, and there was an early increase in survival in patients receiving Rilutek® compared to placebo (Riviere 1998; Chen 2016; Watanabe 2015).

Amyotrophic Lateral Sclerosis (ALS) is a rare neurodegenerative disorder marked by the disruption of upper and lower motor neuron function. Riluzole is an FDA approved drug for treatment of the motor impairments of this disease and is taken by a sizable proportion of ALS patients. Given that dysphagia, or swallowing impairment, occurs in a reported 85% of ALS patients at some point during the disease progression, the ability to ingest riluzole medications can be compromised. Medications that can be easily administered orally without water may improve the quality of life of ALS patients and improve patient care. The riluzole oral soluble film may circumvent the potential inability of an ALS patient to swallow the tablet form of the medication, because the patient or caregiver need only to place the film on the tongue, where the active drug can immediately dissolve into the saliva and be ingested with intentional swallowing or during the normal reflex of swallowing, eliminating the need for swallowing a tablet with liquid or crushing it into soft food. (**Appendix B**) Absorption primarily occurs through the gastrointestinal tract after swallowing.

Therefore, the ROSF product has the potential to improve care and decrease daily burden on patients and caregivers.

6.2. Mechanism of Action

The mechanism by which riluzole exerts its therapeutic effects in patients with ALS is unknown (Rilutek® tablets, US package insert; revision 04/2016). Riluzole decreases the release of glutamate, thereby suppressing excitotoxicity. As oxidative stress and

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excitotoxicity are early events in ALS pathogenesis (Harikrishnareddy 2015), glutamate-mediated excitotoxicity has been postulated to be central to ALS pathogenesis, with motor neuron degeneration mediated by corticomotoneuronal hyperexcitability through transsynaptic anterograde processes (Eisen, 1992). According to Vucic and colleagues (Vucic 2013), because riluzole inhibits glutamatergic transmission, it may be expected that riluzole could exert modulating effects on the transcranial magnetic stimulation parameters of cortical excitability. Such a finding would then provide an objective measure of drug efficacy in ALS. However, the modulating effects of riluzole on cortical function in ALS have been varied. Specifically, while some studies have reported that riluzole partially normalizes cortical excitability (Desiato 1999; Stefan 2001), others have failed to establish any cortical modulating effects (Sommer 1999; Caramia 2000). In addition to direct anti-glutamatergic activity, riluzole appears to exert modulating effects on Na+ channel function (Cheah 2010). Given that increased Na+ channel conductance may contribute to neurodegeneration through Ca2+-mediated processes (Stys 2005, 2007), the Na+ channel blockade by riluzole may provide an additional neuroprotective mechanism in ALS. Of further relevance, riluzole may in part exert its anti-glutamatergic effects by inhibiting Na+ channel conductance and reducing glutamate release from presynaptic nerve terminals (Jimonet 1994; Cheah 2010).

6.3. Pharmacokinetics

According to the Rilutek® US package insert (revision 04/2016), riluzole is well absorbed with average absolute oral bioavailability of approximately 60% (CV=30%). C_{max} occurred at approximately 1.0 hour to 1.5 hours after administration (Le Liboux 1997, 1999). AUC values were linearly related to dose over a dose range of 25 mg to 100 mg. A high fat meal decreases absorption, reducing AUC by about 20% and peak blood levels by about 45%. The mean elimination half-life of riluzole is 12 hours (CV=35%) after repeated doses. With multiple-dose administration, riluzole accumulates in plasma by about twofold, and steady-state is reached in less than 5 days. Riluzole is 96% bound to plasma proteins over the clinical concentration range, mainly to albumin and lipoproteins

A human pilot bioavailability study (Study 1897) comparing ROSF 50mg with Rilutek® tablets 50mg found that the extent of absorption was approximately 14% greater and the rate of absorption was approximately 6% lower for the ROSF without water than for an intact Rilutek® tablet administered with 240 ml of water. When ROSF was administered with 240ml of water, the extent of absorption was approximately 9% greater and the rate of absorption was approximately 12% lower than for the intact Rilutek® tablet administered with 240 ml of water.

The pilot bioavailability study (Study 1897) was an open-label, randomized, single-dose, three-period, four-treatment, four-arm, incomplete crossover study. Sixteen adult, non-smoking subjects were enrolled, and all provided data valid for pharmacokinetic analysis. The four treatments were A: ROSF 50 mg administered without water; B: ROSF 50 mg administered with 240 mL water; C: Rilutek® 50 mg intact tablet administered with 240 mL

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of water; and D: Rilutek® 50 mg tablet, crushed, and administered with 15 mL applesauce. The objective was to compare under fasting conditions the bioavailability of the ROSF 50mg administered with or without water to that of the intact Rilutek® 50 mg tablet, administered with 240 mL of water, i.e., treatments A and B compared with treatment C.

For Treatment A (film without water) vs. Treatment C (intact tablet), Treatment A had approximate 14% higher extent of absorption of riluzole and an approximate 6% lower rate of the absorption of riluzole than Treatment C. The geometric mean T/R ratio for AUC_{0-t} and C_{max} was 113.70% with 90% CI 98.9-130.7%, and 94.36% with 90% CI 74.3-119.7%, respectively. For Treatment B (film with water) vs. Treatment C (intact tablet), Treatment B had approximate 9% higher extent of absorption of riluzole and an approximate 12% lower rate of the absorption of riluzole than Treatment C. The geometric mean T/R ratio for AUC_{0-t} and C_{max} was 108.6% with 90% CI 93.4-126.2%, and 88.1% with 90% CI 68.1-114.0 %, respectively.

Of note, in the pilot bioavailability study (Study 1897), inter-subject variability for ROSF 50mg without water for AUC_{0-t} and AUC_{0-inf} was reported as 25 and 26%, respectively, and for C_{max}, 38%. In contrast, inter-subject variability for the Rilutek® 50mg administered with 240 mL water for AUC_{0-t} and AUC_{0-inf} was reported as 39 and 40%, respectively, and for C_{max}, about 48%. The apparent difference between formulations in inter-subject variability remained when this comparison was limited to the eight subjects in Study 1897 who received both treatments. Intra-subject variability in pilot bioavailability study (Study 1897) was reported as 18 and 19% for AUC_{0-t} and AUC_{0-inf}, respectively, and 32% for C_{max}.

6.4. Safety

The most commonly observed AEs associated with the use of Rilutek® that occurred in at least 2% of patients (50mg twice daily) in pooled Clinical Study 1 and 2, and at a higher rate than placebo were asthenia, nausea, decreased lung function, hypertension, abdominal pain, vomiting arthralgia, dizziness, dry mouth, insomnia, pruritus, tachycardia, flatulence, increased cough, peripheral edema, urinary tract infection, circumoral paresthesia, somnolence, vertigo, eczema. Of those patients who discontinued due to adverse events, the most commonly reported were nausea, abdominal pain, constipation, and ALT elevations.

The following adverse reactions have been identified during the postmarketing use of Rilutek®: Acute hepatitis and icteric toxic hepatitis and renal tubular impairment.

Riluzole Oral Soluble Film (ROSF) was administered to 16 subjects in pilot bioavailability study (Study 1897) that evaluated the bioavailability of a single dose of ROSF 50mg compared to a single dose of Rilutek® 50mg. Sixteen (16) subjects experienced a total of 4 adverse events over the course of the study, all mild in severity. The most common was somnolence, occurring in 2 subjects who received the ROSF and 2 subjects who received the Rilutek® 5 mg dose (Table 1). There were no AEs in clinical laboratory tests and there were no Serious Adverse Events (SAEs), or deaths. All formulations of the test and reference

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products were well tolerated. Inspections of the oral cavity were conducted before application, and after disintegration/dissolution of the ROSF without evidence of local irritation or adverse events related to the application.

Table 1: Adverse Event Listings from Pilot Bioavailability Study 1897 with Riluzole Oral Soluble Film

Subj No.	Period	TRT	Adverse Event	MedDRA Preferred Term	MedDRA System Organ Classification	Onset Date (MMM-DD-YYY)	Onset Time (HH:MM)	Resolution Time (HH:MM)	Time from Dosing (h)	Duration (h)	Severity	Action Taken	Related to Study Drug
07	2	A	Sleepiness	Somnolence	Nervous system disorders	Nov-09-2015	09:30	Nov-09-2015	2.28	1.00	Mild	None	Possible
05	3	C	Sleepiness	Somnolence	Nervous system disorders	Nov-17-2015	08:35	Nov-17-2015	1.43	0.67	Mild	None	Probable
06	1	D	Nausea	Nausea	Gastrointestinal disorders	Nov-02-2015	07:15	Nov-02-2015	0.07	0.25	Mild	None	Probable
10	2	D	Sleepiness	Somnolence	Nervous system disorders	Nov-09-2015	10:30	Nov-09-2015	3.18	0.58	Mild	None	Possible

TRT = Treatment: A = ROSF 50mg administered without water; B = ROSF 50mg administered with 240 mL of water; C = Rilutek® 50mg intact tablet administered with 240 mL of water; D = Rilutek® 50mg crushed with 15ml applesauce.
Source: CSR 1897, Section 16.2.7

7. STUDY OBJECTIVES

7.1. Primary Objectives

Riluzole is FDA-approved for the treatment of patients with Amyotrophic Lateral Sclerosis (ALS). Riluzole extends survival and/or time to tracheostomy. ROSF (MonoSol Rx LLC) is a new formulation of riluzole that allows for rapid dissolution and release of active drug in the oral cavity. Since circumoral paresthesia and dry mouth have been reported with riluzole administered as Rilutek® tablets, the primary objective is to evaluate the effect, if any, of the new ROSF formulation on swallowing safety in subjects with ALS.

STUDY DESIGN

Approximately 30 subjects with ALS will be enrolled and undergo an instrumental evaluation of swallowing safety before and after administration of a single dose of the ROSF formulation containing 50mg of riluzole.

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8. SELECTION AND ENROLLMENT OF SUBJECTS

8.1. Inclusion Criteria and Exclusion Criteria

8.1.1. Inclusion Criteria:

Subjects meeting all of the following criteria may be included in the study:

1. Male or female subjects between 18-80 years of age, inclusive
2. Subjects with a diagnosis of probable or definite ALS in accordance with the Revisited El-Escorial Criteria (Cedarbaum, 1999)
3. Subjects must be currently on an oral diet and able to take foods and liquids by mouth equivalent to a score of 3 or above on the Functional Oral Intake Scale (Crary, 2005).
4. Subjects with no known allergy to barium, riluzole or inactive ingredients* in ROSF
5. Subjects or subject's legally authorized representative must be willing and able to give informed consent/assent and HIPAA authorization.
6. Subjects must have the ability to comprehend and be informed of the nature of the study, as assessed by the PI or Sub-Investigator.
7. Subjects prescribed riluzole at or before the dose of study drug. (The study is open to subjects currently taking riluzole at screening, subjects who are not currently taking riluzole at screening who have taken riluzole in the past, and subjects to be newly started on riluzole (given as ROSF in this study.)
8. Female subjects of childbearing potential must have a negative urine pregnancy test at Screening and Visit 1. Female subjects of childbearing potential (i.e. not surgically sterile, not 2 years postmenopausal, or not with a sterile partner) must have a negative pregnancy test at screening and Visit 1, agree to abstinence, be practicing double barrier contraception or using an FDA approved contraceptive (e.g., licensed hormonal or barrier methods) for greater than 2 months prior to screening visit and commit to an acceptable form of birth control for the duration of the study and for 30 days after participation in the study
9. Availability to volunteer for the entire study duration and willing to adhere to all protocol requirements

*See Investigator Brochure

8.1.2. Exclusion Criteria:

Potential subjects meeting any of the following criteria will be excluded:

1. Subjects who score 2 or below on the Functional Oral Intake Scale (Crary, 2005)

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2. Subjects with a prior swallowing study that has shown a PAS of 3 or greater
3. Subjects with a history of two or more episodes of aspiration pneumonia requiring hospitalization
4. Subjects with a history of clinically significant liver disease, renal disease, or any other medical condition judged to be exclusionary by the investigator
5. Subjects who are unwilling to sign informed consent or subjects who for any other reason in the judgment of investigator are unable to complete the study
6. Female subjects who have a positive urine pregnancy test (βhCG) at screening or Visit 1, are trying to become pregnant or are breastfeeding.
7. Subjects with active cancer within the previous 2 years, except treated basal cell carcinoma of the skin
8. Subjects who have taken any experimental drug within 30 days prior to enrollment or within 5 half-lives of the investigational drug –whichever is the longer period. However, subjects who have previously completed other MonoSol Rx sponsored ROSF clinical studies within the last 30 days prior to enrollment may be eligible for consideration for entry into this study.
9. Subjects with moderate or severe renal impairment as defined by a calculated creatinine clearance of ≤50 mL/minute
10. Subjects currently taking riluzole with ALT levels greater than 5 times upper limit of normal or with evidence of clinical jaundice. (Riluzole should be discontinued in these patients.)
11. Subjects who will be receiving riluzole for the first time who exhibit baseline elevations of several LFTs (especially elevated bilirubin). (These findings at baseline should preclude the use of riluzole including ROSF).
12. Use of potentially hepatotoxic drugs: (e.g., allopurinol, methyldopa, sulfasalazine).
13. Subjects with clinically significant abnormal laboratory values in the judgment of the investigator
14. Use of strong or moderate CYP1A2 inhibitors (e.g., ciprofloxacin, enoxacin, fluvoxamine, methoxsalen, mexiletine, thiabendazole, vemurafenib, zileuton) and CYP1A2 inducers (e.g. rifampin and barbiturates) in the previous 30 days before first drug administration.
15. Anything else that, in the opinion of the investigator, would place the subject at increased risk or preclude the subject's full compliance with or completion of the study

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16. Employee or immediate relative of an employee of the investigator, MonoSol Rx LLC, any of its affiliates or partners, or inVentiv Health.

8.2. Subject Withdrawal

Inclusion in the study is entirely voluntary and subjects may withdraw at any time for any reason. Possible reasons for withdrawal are serious adverse events, adverse events, and subject's choice. Subjects who elect to withdraw from the study after taking study medication but prior to completion of the VFSS 2-PAS will be asked to comply with end of study clinical laboratory evaluation(s). For a complete list of all tests to be performed, see Section 10.3.7, *Laboratory Evaluations*. Subjects who withdraw due to an adverse event will be followed whenever possible until resolution of the adverse event. It may be appropriate for the subject to return to the site 2 weeks after the subject is off study to evaluate for resolution of any adverse events and to receive further information about options for future clinical care. The Investigator will decide the course of action.

8.3. Study Enrollment Procedures

The following screen procedures will be conducted on each potential subject:

- Obtain informed consent as evidenced by subject or subject's legally authorized representative signing an informed consent. Informed consent will be signed prior to any study-related procedures and prior to screening per protocol. Informed consent will be obtained by the site PI and/or his or her designee.
- Record medical history
- Documentation of disease
- Obtain vital signs (temperature, respiratory rate (RR), heart rate (HR), blood pressure (BP), height and weight
- Collect blood and urine for baseline clinical laboratory evaluation(s) and urine pregnancy test (females of childbearing potential only). For a complete list of all tests to be performed, see Section 10.3.7, *Laboratory Evaluations*.
- Complete physical and neurological examinations
- ALS Functional Rating Scale-Revised (ALSFRS-R)
- Eating Assessment Tool-10 (EAT-10)
- Functional Oral Intake Scale (FOIS)
- Collection of pretreatment AEs, if subject receiving riluzole pre study
- Principal Investigator's/Sub-Investigator's review of Inclusion/Exclusion criteria and all screening results/data to assess eligibility of each potential subject

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- Record/Review concomitant medications

Screening procedures will be completed within 28 days of Visit 1.

8.3.1. Subject Recruitment and Retention

Participants will be recruited from patients followed in the neuromuscular programs at The University of Florida. Potential participants will be contacted by the investigators or their staff and invited to participate. These recruitment strategies will include a mechanism by which the subjects can provide their contact information.

8.3.2. Screening Logs

Screening logs to document reasons for ineligibility and reasons for nonparticipation of eligible subjects will be maintained to document number of subjects referred, referral source, number screened, number failed due to ineligibility or nonparticipation of eligible subjects, and reasons for ineligibility or nonparticipation of eligible subjects.

8.3.3. Randomization/Treatment Assignment

Randomization is not applicable. This is an open label swallowing safety and tolerability trial.

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9. DRUG PRODUCT

9.1. Drug Information

Table 2 Drug Information

Treatment	
Drug Name	Riluzole
Strength	50mg
Dosage Form	Oral Soluble Film
Manufacturer	MonoSol Rx LLC
Dose	1 x 50mg

9.2. Handling of Study Drug, Packaging and Labeling

The Sponsor will supply a sufficient quantity of the study drug to allow completion of this study including some excess for replacement if needed. The study drug will be sent to the Investigator packed in individual unit-dose packages. Each unit-dose package will be labeled in English containing at minimum: Protocol Number, Drug Name, Strength, Route of Administration, and statements "Caution: New Drug – Limited by United States Law to Investigational Use Only", "Keep Out of Reach of Children", storage conditions and batch/lot number. The site pharmacies will keep a log of study drug kits received and dispensed identified by subject ID, subject initials, and date dispensed. Study drug will be stored at room temperature in a double-locked room or on-site pharmacy as directed by institutional SOP. The site pharmacist or coordinator as indicated in the delegation log will dispense study drug at the study visit. This is a single dose study. The dose of study drug will not be adjusted.

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the quantity of investigational product administered to study subjects, the quantity received, and the quantity destroyed upon completion of the study. The investigator is responsible for ensuring product accountability records are maintained throughout the course of the study. The inventory record will include details of MonoSol Rx study drug received and dispensed to subjects, batch, and ID numbers will be maintained by the Investigator.

At the completion of the study, all unused study drug, including any excess, will be retained by the Investigator until the authorization to return or destroy is received from the Sponsor. An accounting must be made of any drug deliberately or accidentally destroyed.

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9.3. Concomitant Interventions

All concomitant medications received by a subject during participation in the study will be recorded on the appropriate source documents.

9.3.1. Required Concomitant Medications/Interventions

No concomitant medications or interventions are required per protocol.

The study is open to subjects currently taking riluzole at screening, subjects who are not currently taking riluzole at screening who have taken riluzole in the past, and subjects to be newly started on riluzole (given as ROSF at the start of this study.)

9.3.2. Prohibited Medications/Interventions

Concomitant medications and interventions will be reviewed at screening and Visit 1. The investigator may choose to exclude a subject from participation if a concomitant medication or intervention is judged likely to interfere with the study objectives or to affect the subject's safety.

The following drugs are known to interact with riluzole (Rilutek® tablets US Package Insert; revision 04/2016) and should not be administered with ROSF:

- Agents that may increase riluzole blood concentration; Strong or moderate CYP1A2 inhibitors (e.g., ciprofloxacin, enoxacin, fluvoxamine, methoxsalen, mexiletine, thiabendazole, vemurafenib, zileuton).
- Agents that may decrease riluzole plasma concentrations: CYP1A2 inducers (e.g. rifampin and barbiturates)
- Potentially hepatotoxic drugs: (e.g., allopurinol, methyldopa, sulfasalazine)

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10. STUDY PROCEDURES

10.1. Schedule of Activities

The schedule of study activities is presented in Table 3.

Table 3 Schedule of Activities

Evaluation	Screening	Visit 1
Written Informed Consent	X	
Inclusion/Exclusion Review	X	X[a]
Documentation of Disease	X	
Record/Review Concomitant Medications	X	X[a]
Medical History/ Demographics	X	
Height and Weight	X	
Vital Signs – HR, BP, RR		X[b]
Vital Signs – HR, BP, RR and temperature	X	X[a]
Comprehensive Physical Exam	X	
Brief Physical Exam		X[b]
Neurological Examination	X	
Brief Neurological Exam		X[b]
Eating Assessment Tool-10 (EAT-10)	X	X[a]
Functional Oral Intake Scale (FOIS)	X	X[a]
ALS Functional Rating Scale - Revised (ALSFRS-R)	X	X[a]
Oral Examination	X	X[c]
VFSS 1 - Penetration-Aspiration Scale (pre-dose)		X
VFSS 2 - Penetration-Aspiration Scale (post-dose)		X
Clinical laboratory evaluation(s)hematology, chemistry, urinalysis)[d]	X	X[b]
Urine Pregnancy Test (females of childbearing potential)	X	X[a]
Adverse Event	X	X[c]
Dispense Study Drug (one dose)		X

[a]Before VFSS 1 procedure
[b]After VFSS 2 procedure
[c]Both – before VFSS 1 procedure and after VFSS 2 procedure
[d]See Section10.3.7 *Laboratory Evaluations*

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10.2. Timing of Study Activities

No study procedures will be performed prior to the signing of the Informed Consent Form (ICF). All subjects will sign an ICF prior to undergoing any study tests or procedures.

Visit 1 should occur within 28 days of the Screening Visit.

Inclusion in the study is entirely voluntary and subjects may withdraw at any time for any reason. Possible reason for withdrawal could include serious adverse events, adverse events, and subject's choice. Subjects who elect to discontinue medication will be asked to comply with end of study clinical laboratory evaluation(s) and urine pregnancy test (females of childbearing potential). For a complete list of all clinical laboratory evaluation(s) to be performed, see Section 10.3.7, *Laboratory Evaluations*. Subjects who withdraw due to an adverse event will be followed whenever possible until resolution of the adverse event. It may be appropriate for the subject to return to the site 2 weeks after the subject is off study to evaluate for resolution of any adverse events and to receive further information about options for future clinical care. The Investigator will decide the course of action.

10.2.1. Screening procedures

At the screening visit, potential subjects will be informed about study procedures and will then sign an informed consent form. Inclusion/exclusion criteria will be reviewed and a medical history and full physical examination completed. Vital signs, weight, height and concomitant medications will be recorded. Clinical laboratory tests will be performed including complete blood count (CBC) with differential, electrolytes, BUN, creatinine, ALT, AST, total bilirubin, albumin, and a pregnancy test for women of childbearing potential.

The following procedures will be performed during the screening visit:

- Informed consent
- Inclusion/exclusion assessment
- Documentation of Disease
- Medical history
- Record concomitant medications
- Clinical laboratory evaluation(s)see Section 10.3.7 *Laboratory Evaluations*
- Urine pregnancy test (females of childbearing potential)
- Height and weight
- Vital signs (including temperature)
- Comprehensive physical and neurological examinations including oral examination

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- ALS Functional Rating Scale-Revised (ALSFRS-R)
- Eating Assessment Tool-10 (EAT-10)
- Functional Oral Intake Scale (FOIS)
- Adverse event review, if subject is currently on riluzole

All inclusion and exclusion criteria and clinical laboratory tests will be reviewed by the investigator prior to scheduling the baseline visit (; *Schedule of Activities; Visit 1*). A log will be kept at the site to record all subjects screened for entry into the study. This information will also be captured electronically in the electronic data capture system (EDC). Demographic characteristics of all subjects who are screened will be recorded whether or not they qualify for entry into the study. The reason for non-qualification will be recorded for all subjects who are not eligible. The reason for nonparticipation will also be recorded for subjects who are eligible but choose not to participate in the trial. If a subject fails screening for the study, the subject can be re-screened if the investigator determines it is appropriate to do so. At any time during the study, repeat laboratory tests may be obtained if the investigator or central laboratory believes that a laboratory test result is in error. Additional laboratory tests may also be obtained at any time during the study, at the discretion of the investigator.

10.2.2. On-Study/On-Intervention Evaluations/Procedures

10.2.2.1. Baseline (Day 0,Visit 1):

The baseline visit (Day 0, Visit 1) will include a single dose of study drug. It will be scheduled within 28 days after the screening visit. At this visit, inclusion/exclusion criteria and concomitant medications will be reviewed. Vital signs, brief physical and neurologic examination, as well as study questionnaires and testing will be performed as noted in Table-3; *Schedule of Activities.*

The following documentation and procedures will be performed at Day 0 (Visit 1):

- Adverse event review (before VFSS 1 procedure and after VFSS2 procedure)
- Inclusion/exclusion assessment (before VFSS 1 procedure)
- Concomitant medications (before VFSS 1 procedure)
- Urine pregnancy test for females of childbearing potential (before VFSS 1 procedure)
- Vital signs HR, BP, RR and temperature (before VFSS 1 procedure)
- Vital Signs HR, BP, RR (after VFSS 2 procedure)
- Oral Exam (before VFSS 1 procedure and after VFSS 2 procedure)
- Videofluoroscopy Swallow Study 1 (VFSS 1; pre dose procedure)
- Administer study drug (one dose)
- Videofluoroscopy Swallow Study 2 (VFSS 2; post dose procedure)

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- Brief physical exam (after VFSS 2 procedure)
- Brief neurologic exam (after VFSS 2 procedure)
- Clinical laboratory evaluation(s) see Section 10.3.7 *Laboratory Evaluations (after VFSS 2 procedure)*

Videofluoroscopy Swallow Study (VFSS 1-PAS)

Subjects will undergo a standardized videofluoroscopic swallowing study (VFSS) for direct visualization of the swallowing process and any episodes of penetration or aspiration. The VFSS represents the gold standard swallowing exam to directly visualize swallowing and specifically aspiration during swallowing. After consent has been verified and screens completed, the patient will be seated and will complete a standardized bolus protocol that includes 12 bolus trial presentations in the following order:

1. 5ml thin liquid barium
2. 5ml thin liquid barium
3. 5ml thin liquid barium
4. Regular sip of thin liquid taken from a cup containing 60cc of thin liquid.
5. Consecutive cup sips of remaining thin liquid barium
6. Tablespoon of thin honey consistency barium
7. Tablespoon of thin honey consistency barium
8. Tablespoon of thin honey consistency barium
9. Tablespoon of pudding consistency barium.
10. Tablespoon of pudding consistency barium.
11. Graham cracker with pudding-thick barium.
12. 13 mm barium tablet (EZ-Disk) with water.

A standard 'bail out' criteria used on all VFSS protocols in the Swallowing Systems Core laboratory will be utilized in this study. This represents a standard provision to avoid unnecessary risk to research subjects during VFSS exams and will include cessation of bolus presentations during a specific VFSS test (i.e. either VFSS 1 or VFSS 2) on the third episode of frank aspiration (material entering the airway below the level of the true vocal folds) or residue greater than 75% of either vallecular or pyriform housing that is unable to be cleared by the patient with prompting and strategies. The potential for this to occur is factored into the targeted enrollment of approximately 30 subjects in an effort to complete 25 subjects for the swallowing evaluation consistent with the sample size estimation (Section 13.5.3; *Power*).

The start time and finish time for the standardized bolus protocol will be recorded for both VFSS 1 and VFSS 2.

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Immediately following VFSS 1-PAS, the patient will then be administered ROSF on the dorsum of tongue along the median lingual sulcus, and the time of administration will be recorded (**Appendix B**). Following a three-minute time interval the investigator will confirm that the ROSF has dissolved and VFSS 2-PAS will be performed. If ROSF is not fully dissolved at 3 minutes, start of the second VFSS 2-PAS bolus protocol will be delayed until investigator confirms that ROSF is fully dissolved. The investigator should record whether or not ROSF is fully dissolved at 3 minutes after dosing. In the event that ROSF is not fully dissolved at 3 minutes, the investigator will record the time that it is confirmed that ROSF is fully dissolved.

Videofluoroscopy Swallow Study Test 2-PAS (VFSS 2-PAS)

The identical VFSS standardized bolus protocol exam will be performed provided that the subject did not demonstrate frank, gross and observable silent aspiration during VFSS 1-PAS and provided that the subject's PAS score in baseline test is 7 or below. VFSS will be performed using a Phillips BV Endura fluoroscopic C-arm unit (GE OEC 8800 Digital Mobile C-Arm system type 718074) that is housed within the PI's laboratory and used exclusively for research purposes. Fluoroscopic data will be captured in high resolution at 30 frames per second and in the lateral field of view using a TIMS Dicom (Version 3.2, TIMS Medical, TM, Chelmsford, MA).

The identical standard patient safety bail out criterion will be enforced in VFSS 2. This includes cessation of the specific testing phase on the third episode of frank aspiration or residue greater than 75% of either vallecular or pyriform housing that is unable to be cleared by the patient with prompting and strategies. Once the study is completed, recordings will be saved and digitally backed up for subsequent analyses of the PAS. Although this study is specifically investigating swallowing safety, this bailout criterion will still allow the study of up to three potential episodes of aspiration so that assessing impact on swallowing safety is still feasible while maintaining patient safety.

Missed Visit 1: When a subject fails to appear for scheduled Visit 1, the site will contact the subject. The site will stress the importance of the evaluation and reschedule within the 28-day window if possible.

10.2.3. Study Medication/Intervention Discontinuation Evaluations/Procedures

Inclusion in the study is entirely voluntary and subjects may withdraw at any time for any reason. Possible reason for withdrawal could include serious adverse events, adverse events, and subject's choice. Subjects who decide to discontinue the study either after receiving the VFSS 1-PAS procedure but before receiving study medication or after receiving study drug and before VFSS 2-PAS procedure will be asked to comply with end of study clinical laboratory evaluation(s) see Section 10.3.7 *Laboratory Evaluations*. Subjects who withdraw due to an adverse event will be followed, whenever possible, until resolution of the adverse

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event. It may be appropriate for the subject to return to the site 2 weeks after the subject is off study to evaluate for resolution of any adverse events and to receive further information about options for future clinical care. The Investigator will decide the course of action.

All serious adverse events (SAEs), whether or not the event is deemed drug-related, will be reported on the SAE Report Form by email or fax to the designated Clinical Research Organization, inVentiv Health, within twenty-four hours (24) of the Investigator being aware of SAE (Section 12.3; *Procedures for Reporting Adverse Events*) and inVentiv will report to the Sponsor.

10.2.4. On Study/Off-Intervention Evaluations

Subjects who discontinue the study for any reason either after receiving the VFSS 1-PAS procedure but before receiving study medication or after receiving study drug and before the VFSS 2-PAS procedure will be asked to comply with end of study clinical laboratory evaluation(s); see Section 10.3.7 *Laboratory Evaluations*. Subjects who withdraw due to an adverse event will be followed whenever possible until resolution of the adverse event. It may be appropriate for the subject to return to the site 2 weeks after the subject is off study to evaluate for resolution of any adverse events and to receive further information about options for future clinical care. The Investigator will decide the course of action.

10.2.5. Final On-Study Evaluations

The subject will be followed after Visit #1 for resolution of adverse events. If the subject decided to discontinue the study either after receiving the VFSS 1-PAS procedure but before receiving study medication or after receiving study drug and before VFSS 2- PAS procedure, the subject will be asked to comply with end of study clinical laboratory evaluation(s); see Section 10.3.7 *Laboratory Evaluations*.

10.2.6. Off-Study Requirements

Subjects who withdraw due to an adverse event will be followed whenever possible until resolution of the adverse event. It may be appropriate for the subject to return to the site 2 weeks after the subject is off study to evaluate for resolution of any adverse events and to receive further information about options for future clinical care. The Investigator will decide the course of action.

10.2.7. Pregnancy

Women who are pregnant will not be enrolled in the study. Riluzole has not been studied in pregnancy and the Rilutek® US Package Insert notes that based on animal studies riluzole may cause fetal harm. Following administration of study drug, any known cases of pregnancy in female subjects or female partners of male subjects, will be reported until 30 days after the subject completes or withdraws from the study. The pregnancy will be reported immediately by phone and by faxing/emailing a completed Pregnancy Report to the

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Sponsor (or designee) within 24 hours of knowledge of the event. (Section 12.3; *Procedures for Reporting Adverse Events*)

10.3. SPECIAL INSTRUCTIONS AND DEFINITIONS OF EVALUATIONS

10.3.1. Protocol Deviations

Missed visits and any procedures not performed (not attempted) for any reason will be reported as protocol deviations. Details regarding any deviations will be documented.

10.3.2. Documentation of Amyotrophic Lateral Sclerosis

To be eligible for participation in this trial, participants must have ALS defined as probable or definite ALS in accordance with the Revisited El-Escorial Criteria (Cedarbaum, 1999). These criteria will be clearly designated on source documentation and in the electronic case report forms (eCRFs).

10.3.3. Medical History

A comprehensive medical history will be obtained at the screening visit and reviewed for any exclusionary criteria.

10.3.4. Treatment History

Medications will be reviewed for concomitant therapies that would be exclusionary.

10.3.5. Concomitant Medications/Treatments

Current medications will be reviewed for contraindicated therapies.

10.3.6. Clinical Assessments

10.3.6.1. Physical and Neurological Examination

Subjects will undergo a comprehensive physical and neurological examination at screening, and a brief physical and neurological examination at Visit 1 following the second VFSS.

The comprehensive physical examination will include complete vital signs, weight, height, general appearance, and evaluation of systems: head, ears, eyes, nose, and throat; respiratory; abdomen; lymph nodes; spine; skin; cardiovascular; and extremities. The brief general physical examination will include abbreviated vital signs (blood pressure, heart rate, respiratory rate), and examination of the cardiovascular and respiratory systems and abdomen. Other elements may be included depending on symptoms or physical findings.

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The comprehensive neurological examination will include (as permitted by the patient's capabilities) cranial nerves 2-12, muscle tone and strength, tendon reflexes and plantar response, sensory function (pain, light touch, position, vibration), coordination (finger-nose), and gait. The brief neurological examination will include cranial nerves 2-12, muscle strength, tendon reflexes, plantar response, and sensory function (pain, light touch, position, vibration). Other elements may be included depending on symptoms or physical findings

10.3.6.2. Primary Outcome Variable: Videofluoroscopy Swallow Study – Penetration Aspiration Scale (VFSS - (PAS)).

The primary objective is to evaluate the effect, if any, of the new ROSF formulation on swallowing safety in subjects with ALS. The primary outcome is the difference in PAS Scores obtained before and after ROSF administration.

The validated penetration aspiration scale (PAS) is a direct measure of swallowing safety. The PAS is an 8-point validated scale of swallow safety that takes into account both degree/level of airway invasion during swallowing and the patient's response to the penetration or aspiration episode. The PAS scale is provided in Table 4 (Rosenbek, 1996) with VFSS lateral image examples recorded and analyzed from our laboratory to provide examples of each type of swallow on the right-hand panel.

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Table 4 Penetration Aspiration Scale (PAS)

Airway Safety Group	PAS Score	Definition
SAFE	1	Material does not enter airway.
	2	Material enters the airway, remains above VF, and is ejected from airway.
UNSAFE	3	Material enters the airway, remains above VF and is not ejected from airway.
	4	Material enters the airway, contacts VF and is ejected from airway.
	5	Material enters the airway, contacts VF and is not ejected from airway.
	6	Material enters the airway, passes below VF and is ejected into the larynx or out of airway.
	7	Material enters the airway, passes below VF and is not ejected from airway despite effort.
	8	Material enters the airway, passes below VF and no effort is made to eject.

The inclusion criteria are developed to focus the study on a cross section of ALS subjects. Exclusion criteria exclude subjects with certain medical conditions, with allergies to barium or study drug, and females who are pregnant or breastfeeding.

The primary aim of this study is to assess swallowing safety with the new ROSF formulation.

10.3.7. Laboratory Evaluations

Blood and urine specimens will be collected by qualified study center personnel at screening and visit 1 as described under *Section 10.0 Study Procedures* and sent to the lab for analysis. Clinical laboratory evaluation(s) are conducted at the screening visit and Visit 1(after VFSS 2 procedure). A urine pregnancy test (females of child bearing potential only) will be conducted at the screening visit and at Visit 1 (before VFSS 1 procedure). The clinical laboratory evaluation(s) are presented in Table 5.

If the subject decided to discontinue the study either after receiving the VFSS 1-PAS procedure but before receiving study medication or after receiving study drug and before the VFSS 2- PAS procedure, the subject will be asked to comply with end of study clinical laboratory evaluation(s) presented in Table 5.

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Table 5 Clinical Laboratory Evaluation(s)

Hematology	Serum Chemistry	Urine
Complete Blood Count with Differential	Electrolytes	Urinalysis
	BUN	Pregnancy Test (females of childbearing potential)
	Creatinine	
	ALT	
	AST	
	Total Bilirubin	
	Albumin	

Abnormal laboratory test results or a positive urine pregnancy test will be flagged by the laboratory. All clinically important abnormal laboratory tests occurring during the study will be repeated if appropriate and followed until resolution (return to normal or baseline values) or stabilize, or until they are considered by the Investigator to be no longer clinically significant.

10.3.8. ALS Functional Rating Scale – Revised (ALSFRS-R) Questionnaire

The ALSFRS-R is a quickly administered (5 minute) ordinal rating scale (ratings 0-4) used to determine subjects' assessment of their capability and independence in 12 functional activities/questions (Cedarbaum, 1999). All 12 activities are relevant in ALS. Initial validity was established by documenting that in subjects with ALS, change in ALSFRS-R scores correlated with change in strength over time, was closely associated with quality of life measures, and predicted survival (**Appendix A**). The test-retest reliability is greater than 0.88 for all test items. The advantages of the ALSFRS-R are that the categories are relevant to ALS; it is a sensitive and reliable tool for assessing activities of daily living function in subjects with ALS; and it is quickly administered. In a recent trial employing the ALSFRS as a secondary outcome measure, placebo-treated patients showed a decline of 0.92 units per month, with a standard error of 0.08. With appropriate training the ALSFRS-R can be administered with high inter-rater reliability and test retest reliability.

10.3.9. Eating Assessment Tool -10 (EAT-10)

EAT-10: The Eating Assessment Tool-10, is a validated 10-item patient report scale of perceived swallowing impairment (Belafsky et al. 2008). The EAT-10 uses a 5-point ordinal rating scale where a patient rates their perceived degree of impairment for each item from 0 (no impairment) to 4 (severe impairment) for a total range of scores between 0 (no perceived swallowing impairment) to 40 (severe impairment) (**Appendix C**). The P.I of this study

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recently determined that the EAT-10 was sensitive to identify ALS patients with severe dysphagia including aspiration. A Receiver Operating Curve analysis revealed that a cut point of 8 on the EAT-10 yielded a sensitivity of 86%, specificity of 72%, likelihood ratio of 3.1, and negative predictive value of 95.5% for detecting aspiration in ALS (Plowman et al., 2016).

10.3.10. Functional Oral Intake Scale (FOIS)

The FOIS is a simple 7 point scale that describes the subject's functional status with respect to oral intake, ranging from 1 (No oral intake) to 7 (Total oral intake with no restrictions) (**Appendix D**) (Crary, 2005).

10.3.11. Subject Adherence Assessments

Adherence to study requirements and compliance with concomitant medication restrictions will be assessed Visit 1 through direct questioning by study personnel.

10.3.12. Physical and Neurological Examination

Subjects will undergo a comprehensive physical and neurological examination at screening, and a brief physical and neurological examination at Visit 1 following the second VFSS.

The comprehensive physical examination will include complete vital signs, weight, height, general appearance, and evaluation of systems: head, ears, eyes, nose, and throat; respiratory; abdomen; lymph nodes; spine; skin; cardiovascular; and extremities. The brief general physical examination will include abbreviated vital signs (blood pressure, heart rate, respiratory rate), and examination of the cardiovascular and respiratory systems and abdomen. Other elements may be included depending on symptoms or physical findings.

The comprehensive neurological examination will include (as permitted by the patient's capabilities) cranial nerves 2-12, muscle tone and strength, tendon reflexes and plantar response, sensory function (pain, light touch, position, vibration), coordination (finger-nose), and gait. The brief neurological examination will include cranial nerves 2-12, muscle strength, tendon reflexes, plantar response, and sensory function (pain, light touch, position, vibration). Other elements may be included depending on symptoms or physical findings.

11. SAFETY AND ADVERSE EVENTS

The PI will carefully monitor each subject throughout the study for possible AEs. All AEs will be documented on CRFs designed specifically for this purpose. All AEs will be reported whether serious or non-serious.

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11.1. Adverse Experience Reporting and Follow Up

Subjects will be instructed to inform clinic personnel of any untoward medical symptoms and/or events that may arise during the course of the study. If an adverse event is experienced by a subject, then the subject will be questioned concerning symptoms that may have occurred after the administration of the study drug. The incidence, severity and duration of all AEs will be recorded according to the following scale:

Mild	Adverse event resulting in discomfort, but not sufficient to cause interference in normal daily activities
Moderate	Adverse event resulting in discomfort that is sufficient to cause interference in daily activities.
Severe	Adverse event resulting in discomfort causing an inability to carry out normal daily activities

Subjects who withdraw due to an adverse event will be followed whenever possible until resolution of the adverse event. It may be appropriate for the subject to return to the site 2 weeks after the subject is off study to evaluate for resolution of any adverse events and to receive further information about options for future clinical care. The Investigator will decide the course of action.

11.2. Assessing Relationship to Study Drug

The Principal Investigator/Sub Investigator will assess the relationship of all adverse reactions to the drug, using the following scale:

Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and which other drugs, chemicals or underlying disease provide plausible explanation.

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Unrelated	This category is applicable to AEs which are judged to be clearly and incontrovertibly due to extraneous causes (diseases, environment, etc.) and do not meet the criteria for drug relationship listed for the above mentioned conditions.

Any AEs, whether serious or non-serious, will be monitored throughout the study and followed to resolution, when possible, regardless of whether the subject is still participating in the study. Subjects who withdraw due to an adverse event will be followed whenever possible until resolution of the adverse event. It may be appropriate for the subject to return to the site 2 weeks after the subject is off study to evaluate for resolution of any adverse events and to receive further information about options for future clinical care. The Investigator will decide the course of action.

11.3. Procedures for Reporting Adverse Events

Subjects will be instructed to inform clinic personnel of the AEs that may arise during the course of the study. Treatment of any AEs will be administered under the direction of the Investigator.

All symptoms will be recorded by clinic staff and will be reviewed by the Investigator or Sub-Investigator prior to any subsequent dosing.

When appropriate, medical tests and examinations will be performed to document resolution of the event(s).

Adverse events will be coded into the Preferred Term (PT), classified according to the current version of Medical Dictionary for Regulatory Activities (MedDRA) with System Organ Classification (SOC) and reported with severity, duration, onset time and relationship to study drug and action taken.

Female subjects of child-bearing potential must have a negative pregnancy test at all visits. Following administration of study drug, any known cases of pregnancy in female subjects or female partners of male subjects, will be reported until 30 days after the subject completes or withdraws from the study. The pregnancy will be reported immediately by phone and by faxing/emailing a completed Pregnancy Report to the Sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as a serious adverse event (SAE); however the Investigator will follow the subject until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of pregnancy. The Investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up Pregnancy Report. If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented] stillbirth, neonatal death, or congenital anomaly), the Investigator will report

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the event by phone and by faxing a completed SAE form to the Sponsor (or designee) within 24 hours of knowledge of the event.

All serious adverse events (SAEs), whether or not the event is deemed drug-related, will be reported on the SAE Report Form by email or fax to the designated Clinical Research Organization, inVentiv Health within twenty-four hours of the Investigator being aware of SAE and inVentiv will report to the sponsor.

The safety address where SAE report forms and other SAE related documents should be sent is:

Fax No. +1 866 856 1649

Email: In case of emergency or fax failure the report can also be submitted by email to **saereceipt.international @inventivhealth.com**

If notification cannot be made via these means due to technical delivery problems, initial notification may be made by phone, using the inVentiv Health GSPV "SAE Hotline" number. A telephone call to the SAE hotline does not substitute for the site's responsibility to submit a written SAE Report Form to inVentiv Health SAEs reported via the Hotline number must be followed with the SAE report the same day.

Hotline No.: 888-750-8020

In the event of any fatal or life-threatening SAE, the investigator must also inform a Medical Monitor at inVentiv Health by telephone or email:

Jane Williams, MD MPH Medical Director, Neuroscience Medical and Scientific Affairs Tel: +1 978 501-0714 Email: jane.williams@inventivhealth.com	Dr. Marcel Reichert Medical Director Tel: 650-554-1706 Cellular: 650-550-1706 Email: marcel.reichert@inventivhealth.com

The Investigator will be responsible for notifying the IRB. The Sponsor will be responsible for notifying the regulatory agencies, as appropriate.

If a subject experiences a non-serious Adverse Event:

- All clinical adverse events are recorded in the CRFs designed specifically for this purpose. It is important to report all AEs, especially those that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

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- The site should fill out the CRF and enter the non-serious AE information into the online Adverse Event Reporting System within 5 working days/7 calendar days of the site learning of a new AE or receiving an update on an existing AE.

Expected adverse events for riluzole are provided in Section 6.4; *Safety.*

12. CRITERIA FOR INTERVENTION DISCONTINUATION

A subject will be discontinued from the study under the following circumstances:

- If the subject is hemodynamically unstable
- If discontinuation is recommended by treating physician
- At the subject's request

13. STATISTICAL CONSIDERATIONS

13.1. General Design Issues

This open label, single center, single dose study has been designed to evaluate the effect, if any, of ROSF, a new formulation riluzole, on swallowing safety in ALS. The study will be performed at single center in Gainesville at the University of Florida. The anticipated time from study enrollment until completion of data analyses is approximately 9 months. The site is anticipated to enroll approximately 3-4 ALS subjects per month for a total of 8 months and data analysis of raw PAS scoring is anticipated to be conducted over one month. The inclusion criteria are intended to provide a representative cohort of subjects with ALS who are currently on an oral diet and able to take foods and liquids by mouth, equivalent to a score of 3 or above on the Functional Oral Intake Scale (Crary, 2005). Eligibility criteria exclude subjects with certain medical conditions, allergies to study drug or females that are pregnant or breastfeeding.

The primary aim of this study is to assess swallowing safety with the new ROSF formulation.

13.2. Outcomes

13.2.1. Primary Outcome:

The primary objective is to evaluate the effect, if any, of the new ROSF formulation on swallowing safety in subjects with ALS. The primary outcome is the within subject difference in PAS Scores obtained before and after ROSF administration.

13.3. Sample Size and Accrual

The estimated sample size for this study is 25 completed subjects. Approximately 30 subjects will be enrolled. Participants will be recruited from patients followed in the neuromuscular

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program at the University of Florida. Interested participants will be contacted by the investigators or their staff and invited to participate. These recruitment strategies will include a mechanism by which the subjects can provide their contact information.

13.4. Data Monitoring

Data Monitoring will be conducted according to Good Clinical Practice and applicable government regulations. The investigator agrees to allow monitors access to the clinical supplies, dispensing and storage areas, and the clinical files of the study subjects and, if requested, agrees to assist the monitors.

Safety monitoring will include careful assessment and appropriate reporting of adverse events. Medical monitoring will include contemporaneous assessment of serious adverse events.

13.5. Data Analyses

13.5.1. Penetration Aspiration Scale (PAS)

Following the examination, each recorded swallow trial will be spliced by bolus trial and further by individual swallow and coded for subsequent evaluation. This will include splicing and coding of each bolus trial per patient (n=12 per VFSS test). Further, each individual swallow within a bolus trial will be analyzed (this can range between 1 to 7 swallows per bolus trial). Frame-by-frame analysis at 30 frames per seconds will be utilized. Two independent, blinded, and experienced raters from the PI's laboratory will perform analyses. Discrepancies between raters will be flagged and resolved at a consensus meeting and three swallows from each evaluation will be repeat rated at random for evaluation of intra-rater reliability.

13.5.2. Statistical Analysis

The within subject difference in PAS scores (before and after ROSF) is the primary outcome to assess swallowing safety of ROSF in subjects with amyotrophic lateral sclerosis. Data will be analyzed using the non-parametric Wilcoxon Signed-Rank Test. Alpha will be set at 0.05. Analysis across each swallowing trial will be performed, providing 12 bolus stimuli trials and approximately 35 swallows and PAS scores for each swallow within each participant (across various textures and swallowing complexities) to ensure a comprehensive exam across a variety of liquid volumes, textures and consistencies). A sample size of 25 subjects is estimated to provide 80% power to detect an intra-subject difference of one point on the PAS at the 0.05 level (two-tailed). Additional details will be provided in the statistical analysis plan.

Depending on the study enrollment rate, the Sponsor may elect to perform an interim analysis using available data from the subset of subjects who have completed the study at that time. The results of this interim analysis will be used only for internal planning and

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possibly for sharing with regulatory authorities. The results of the interim analysis will have absolutely no influence on the subsequent conduct of the study.

Summary Statistics will be provided for the following:

- Demographic information
- Type, incidence, and severity of adverse events
- Physical and neurological examinations including oral examination
- Vital signs (heart rate, blood pressure, respiration rate, temperature),
- Clinical laboratory evaluation(s) and urine pregnancy test (females of childbearing potential)
- ALS Functional Rating Scale – Revised (ALSFRS-R)
- Eating Assessment Tool -10 (EAT-10)
- Functional Oral Intake Scale (FOIS)

13.5.3. Power

Sample size for the present study was determined for a within-subject design (repeated measures, same subjects in VFSS 1-PAS and VFSS 2-PAS) at power = 80% and alpha = 0.05 (G*Power Version 3.1.9.2), assuming a correlation = 0.6 across the two measurements. A sample size of n=25 would be able to detect at least 1.0 point difference, effect size 0.6, in PAS scores between VFSS 1-PAS and VFSS 2-PAS (before and after ROSF). It is anticipated that approximately 20% of recruited ALS subjects will grossly aspirate during VFSS 1-PAS and therefore not have a VFSS 2-PAS performed (for both safety reasons and also because VFSS 2-PAS would not yield any useful data due to a ceiling effect). Therefore a total of 30 individuals with ALS will be recruited and enrolled to account for this potential.

The null hypothesis is no difference in the PAS scores before and after administration of the study medication (i.e. PAS scores for VFSS 1-PAS and VFSS 2-PAS).

14. PROTOCOL AMENDMENTS AND STUDY TERMINATION

All revisions and/or amendments to this protocol must be documented and approved in writing by the Investigator and Sponsor. If the revision/amendment will affect subject safety and/or study design, then the amendment will be re-submitted to the IRB Authorities for approval. Administrative changes (i.e., typographical errors, discrepancies, clarifications) will also be submitted to the IRB, but may not require approval. A copy of the IRB's approval documents will be included in the final report.

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It is the Sponsor's responsibility to submit, or to assign responsibility to submit, all revisions and amendments to the appropriate regulatory authorities, when necessary.

For revisions or amendments to the protocol that substantially alter the study design after initiation of the study, the Investigator and Sponsor will decide whether a revised ICF will be needed for continued participation.

The Sponsor and Principle Investigators reserve the right to discontinue the study at the clinical study site for safety or administrative reasons at any time. Should the study be terminated and/or the clinical study site closed for any reason, all documentation and study medication pertaining to the study must be returned to the Sponsor or its representative

15. ETHICAL CONSIDERATIONS

15.1. Basic Principles

This research will be carried out in accordance with Good Clinical Practice (GCP) as set out by the International Council for Harmonization (ICH), the basic principles defined in the U.S. Code of Federal Regulations (21 CFR Part 312), the Belmont Report, Directive 2001/20/EC (Europe), The Tri-Council Policy Statement and the principles enunciated in the most recent version of the World Medical Association Declaration of Helsinki.

15.2. Institutional Review Board Review and Informed Consent

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB responsible for oversight of the study. A signed consent form, approved by the IRB, will be obtained from the subject by the site PI and/or their IRB-approved designee.

For subjects who cannot provide consent for themselves, such as those below the legal age, a parent, legal guardian, or person with power of attorney, must sign the consent form; additionally, the subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks associated with the study.

Written informed consent will be obtained from each participant before any study-specific procedures or assessments are performed and after the aims, methods, anticipated benefits and potential hazards are explained. The participant's willingness to participate in the study will be documented in writing in a consent form, approved by the IRB, which will be signed by the participant and Investigator or designee with the date of signature indicated. The Investigator will keep the original consent forms and copies will be given to the participants. It will also be explained to the participants that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study in a language understandable to the participant will

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be given to all participants. HIPAA guidelines for confidentiality and the principles of medical ethics will be adhered to during the study.

It is the Sponsor's responsibility to submit, or to assign responsibility to submit, all informed consents and revisions to the appropriate regulatory authorities, when necessary.

15.3. Delegation of Investigator Tasks

The Investigator may delegate tasks as appropriate to individuals who are qualified by education, training and experience (and state licensure where relevant) to perform the delegated task, as described in the FDA Guidance for Industry on Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects; October 2009.

15.4. Subject Confidentiality

All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the clinical study site will be identified only by the study specific Subject Identification Number (SID) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using study specific SIDs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the sponsor, or the sponsor's designee.

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Appendix A
ALS Functional Rating Scale – Revised[1]

ALSFRS-R

(ALS Functional Rating Scale)

** Please circle the number of your answer

Patient Name_____ MRN#_____ Date_____

1. Speech 4 normal speech processes 3 detectable speech disturbance 2 intelligible with repeating 1 speech combined with non-vocal communication 0 loss of useful speech	**7. Turning in bed and adjusting bed clothes** 4 normal 3 somewhat slow or clumsy, needs no help 2 can turn alone or adjust sheets with great difficulty 1 can initiate, cannot turn or adjust sheets 0 helpless
2. Salivation 4 normal 3 slight but definite excess of saliva in mouth, may have nighttime drooling 2 moderately excessive saliva, may have minimal drooling 1 marked excess of saliva with some drooling 0 marked drooling, requires constant tissue	**8. Walking** 4 normal 3 early ambulation difficulties 2 walks with assistance 1 non-ambulatory functional movement only 0 no purposeful leg movement
3. Swallowing 4 normal eating habits 3 early eating problems, occasional choking 2 dietary consistency changes 1 needs supplemental tube feedings 0 NPO (exclusively parenteral or enteral feedings.	**9. Climbing Stairs** 4 normal 3 slow 2 mild unsteadiness or fatigue 1 needs assistance 0 cannot do
4. Handwriting 4 normal 3 slow or sloppy, all words legible 2 not all words legible 1 able to grip pen, unable to write 0 unable to grip pen	**R-1. Dyspnea (difficult or labored breathing; breathlessness or shortness of breath)** 4 none 3 occurs when walking 2 occurs with one or more: eating, bathing, dressing 1 occurs at rest, either sitting or lying 0 significant difficulty, considering mechanical support
5a. Cutting food and handling utensils (patients <u>without</u> gastrostomy) 4 normal 3 somewhat slow and clumsy, needs no help 2 can cut most foods, slow or clumsy, some help needed 1 foods cut by someone else, can still feed slowly 0 needs to be fed	**R-2. Orthopnea (difficult or labored breathing that occurs when laying flat and is relieved by elevating the head and chest with two pillows)** 4 normal 3 some difficulty sleeping, d/t shortness of breath, does not routinely use more than two pillows 2 needs extra pillows to sleep (>2) 1 can only sleep sitting up 0 unable to sleep
5b. Cutting food and handling utensils (patients <u>with</u> gastrostomy) 4 normal 3 clumsy, able to perform manipulations 2 some help needed with closures and fasteners 1 provides minimal assistance to caregiver 0 unable to perform any aspect of task	**R-3. Respiratory Insufficiency** 4 none 3 intermittent use of BiPAP 2 continuous use of BiPAP at night 1 continuous use of BiPAP day and night 0 invasive mechanical ventilation by intubation/trach
6. Dressing and hygiene 4 normal 3 independent self care with effort or decreased efficiency 2 intermittent assistance or substitute methods 1 needs attendant for self care 0 total dependence	**Total Score _____/ 48**

[1] Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: A revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci 1999; 169(1-2): 13–21

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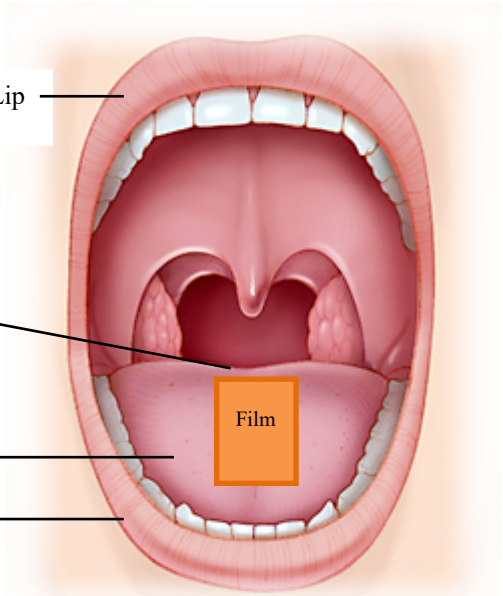
APPENDIX B

Placement Diagram and Instructions for Use

Riluzole Oral Soluble Film

Placement Diagram



Placement on the top surface (Dorsal Aspect of the Tongue):

Riluzole Oral Soluble film is to be centered on the top surface of the tongue, along the midline, with the posterior edge of the film along the posterior edge of the tongue as illustrated by the Figure.

Ensure film is completely adhered to the lingual surface.

Note: Figure is for illustrative purposes and not drawn to scale.

Figure: Placement of ROSF 50 mg on the top surface (dorsal aspect) of the tongue.

Instructions for Use:

1. Keep the Riluzole Oral Soluble Film in the foil pouch until ready for use and use it right way after it is taken out of the pouch.
2. Make sure your hands are dry.
3. Fold the pouch along the dotted line to expose the tear notch. Tear or cut with scissors.
4. Put the Riluzole Oral Soluble Film on the center of the top surface of the tongue immediately after taking it out of the pouch and close the mouth. It will dissolve in minutes. Administration with liquid is not necessary.
5. While the film is dissolving do not chew, talk, swallow the film, or move the film from placement.
6. As the film dissolves swallow your saliva in the normal manner.

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APPENDIX C

Eating Assessment Tool[2] (EAT-10)

Please answer each of the ten questions listed below by **circling the appropriate number** that you feel best describes how you feel, with: 0= no problem at all; 4= severe problems.

Circle the appropriate response:

To what extent are the following scenarios problematic for you?	0= No Problem 4=Severe Problem				
1. My swallowing problem has caused me to lose weight.	0	1	2	3	4
2. My swallowing problem interferes with my ability to go out for meals.	0	1	2	3	4
3. Swallowing liquid takes extra effort.	0	1	2	3	4
4. Swallowing solids takes extra effort.	0	1	2	3	4
5. Swallowing pills takes extra effort.	0	1	2	3	4
6. Swallowing in painful.	0	1	2	3	4
7. The pleasure of eating is affected by my swallowing.	0	1	2	3	4
8. When I swallow food sticks in my throat.	0	1	2	3	4
9. I cough when I eat.	0	1	2	3	4
10. Swallowing is stressful.	0	1	2	3	4
Total EAT-10					

[2] Belafsky PC, Mouadeb DA, Rees CJ, Pryor JC, Postma GN, Allen J, and Leonard RJ. Validity and reliability of the Eating Assessment Tool (EAT-10). Ann Otol Rhinol Laryngol 117: 919-924, 2008.

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APPENDIX D

Functional Oral Intake Scale (FOIS)

Functional Oral Intake Scale[1]

TUBE DEPENDENT (levels 1-3)

1 No oral intake
2 Tube dependent with minimal/inconsistent oral intake
3 Tube supplements with consistent oral intake

TOTAL ORAL INTAKE (levels 4-7)

4 Total oral intake of a single consistency
5 Total oral intake of multiple consistencies requiring special preparation
6 Total oral intake with no special preparation, but must avoid specific foods or liquid items
7 Total oral intake with no restrictions

[1] Crary MA, Carnaby-Mann GD, Groher ME. Initial psychometric assessment of a functional oral intake scale for dysphagia in stroke patients. *Arch Phys Med Rehabil* 2005;86:1516-1520.

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