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

Statistical Analysis Plan for Study 17MO1R-0012, 12-Oct-2018

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STATISTICAL ANALYSIS PLAN

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

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inVentiv Health Clinical

Approval

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

Protocol No: 17MO1R-0012, Amendment I

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised
BMI	Body Mass Index
BP	Blood Pressure
CRF	Case Report Form
CSR	Clinical Study Report
EAT	Eating Assessment Tool
FDA	Food and Drug Administration
FOIS	Functional Oral Intake Scale
H	Above Normal Range
HR	Heart Rate
ICF	Informed Consent Form
L	Below Normal Range
Max	Maximum (equivalent to Max.)
MedDRA®	Medical Dictionary For Regulatory Activities
Mg	Milligram
Min	Minimum (equivalent to Min.)
N	Number of observations
PAS	Penetration Aspiration Scale
PT	MedDRA® Preferred Term
ROSF	Riluzole Oral Soluble Film
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System
SD	Standard Deviation
SOC	MedDRA® System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
VFSS	Videofluoroscopic Swallowing Study
WHO DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) is intended to give a detailed description of the summaries and the analyses that will be generated for the present study by inVentiv Health Clinical. Analyses specified in this plan are based on Protocol 17MO1R-0012 Version 2.0, Amendment I, dated 18 October 2017. Safety and tolerability analyses will be described.

The original plan has changed as described below. Further details are documented in the remainder of this document. These changes will also be described in the clinical study report (CSR).

Top-line clinical results from the Videofluoroscopic Swallowing Study (VFSS) for the first 7 completed patients were presented to the Food and Drug Administration (FDA) on Sept 10 2018. At that time, two additional patients had been enrolled but had not yet undergone the VFSS. On Sept 12 2018, the FDA agreed with the Sponsor that due to the lack of any signal of detrimental effect on VFSS after one dose of study drug, the study would be terminated after the completion of 9 patients (the seven completed by Sept 10 and the two additional patients in screening at that time). In addition to the lack of signal of any harmful effect, the Agency and the Sponsor took into account the difficulty and hardship involved for these disabled patients in participating in the study, the potential risks of participation (including possible reaction to barium, potential for aspiration, and exposure to radiation), and the fact that the participating patients would derive no direct benefit for participation.

When applicable, all methodology and related processes will be conducted according to Standard Operating Procedures (SOPs) of InVentiv Health Clinical.

2. STUDY OBJECTIVE

The 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.

3. STUDY DESIGN

3.1 General Design

This is a single site, phase 2, single dose, open-label safety study to evaluate the effect of Riluzole Oral Soluble Film (ROSF) on swallowing safety in individuals with Amyotrophic Lateral Sclerosis (ALS). The original plan called for approximately 30 subjects with ALS to be enrolled, with a goal of 25 completed subjects after allowance for dropouts. These subjects were to 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 (VFSS) to afford direct visualization of the swallowing process and any episodes of penetration or aspiration will be quantified using the validated Penetration Aspiration Scale (PAS). Subjects will undergo a standardized protocol that includes 11 bolus stimuli presentations of different liquid and food materials to test the swallow across a continuum of textures and materials. Immediately following this, subjects will be given a single dose of ROSF 50 mg, 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.

The study visit duration is expected to be approximately 30 days from time of screening to completion of study.

3.2 Treatment description

A single dose of 50 mg Riluzole Oral Soluble Film (ROSF) will be administered to the subject, placed on the median lingual sulcus of the dorsum of the tongue. The treatment administered in this study is presented in Table 3-1

Table 3-1 Treatment Description

Treatment	Description
Riluzole 50 mg Oral Soluble Film	1 x 50 mg Riluzole Oral Soluble Film

This is an open-label study and neither subjects nor clinic staff will be blinded.

4. 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 Section 6.5.4 *Laboratory Parameters*

5. ANALYSIS POPULATION

The analysis of safety parameters will be based on the safety population detailed in Section 5.1 below.

5.1 Safety Population

The safety population is defined as the group of subjects who receive the study medication.

6. STATISTICAL METHODOLOGY

6.1 Statistical and Analytical Issues

6.1.1 Statistical Methods

Percentages and Decimal Places

If not otherwise specified, the following rules are applied, with the exception of listings:

- Percentages will be presented to 1 decimal point.
- Percentages equal to 0 or 100 will be presented as such without a decimal point.
- Minimum and maximum will be presented with the same precision as the original values and, mean, standard deviation, and median will be presented with one more decimal place than the original values.

Software to be used for Analysis

The inferential statistical analyses, the safety data tables and listings will be created using SAS®, software version 9.4 or higher.

6.1.2 Handling of Dropouts and Missing Data

Missing values will not be imputed. The shifts required for the shift tables will already be included in the ADaM dataset.

6.1.3 Pooling of Investigative Sites

Pooling of investigative sites is not applicable for this study.

6.2 Determination of Sample Size

The original protocol specified that approximately thirty (30) subjects with ALS would be recruited to obtain a final sample size of at least 25 completed. As previously noted, the Sponsor and FDA have agreed to terminate the study with a completed sample size of 9 subjects.

6.3 Subject Characteristics

6.3.1 Subject Disposition

Subject disposition will be summarized as number and percentage of subjects in the treatment group for the below listed categories.

- Screened and screen failure subjects
- Enrolled and not enrolled subjects
- Dosed and not dosed subjects
- Number of subjects completed the study
- Number of subjects discontinued with reason

Subject disposition information will be listed. In addition, subjects who did not complete the VFSS will also be presented in this listing, including early termination reason and date and time of discontinuation.

For subjects enrolled, not enrolled and screen failures, the percentage denominator will be the number of screened subjects. For all other calculations, the percentage denominator will be the number of subjects dosed (safety population).

6.3.2 Protocol Deviations

All protocol deviations will be collected on CRF and will be listed by subject including start date, end date and impact of deviation. Study day will be presented along with start and end date of deviation.

6.3.3 Background and Demographic Characteristics

Descriptive statistics (sample size, mean, median, standard deviation [SD], minimum [Min] and maximum [Max]) will be presented for continuous variables: age, height, weight and body mass index [BMI]. Frequency counts and percentages will be tabulated for categorical variables: age group (<18, 18-40, 41-65, and > 65 years), gender, ethnicity, and race.

Results will be presented for the safety population.

All demographic characteristics will be listed by subject.

6.3.4 Study Drug Administration

The study drug administration details (start/end date, start/end time) will be listed by subject. The dosing time will be set to the time the film is placed on the center of the top surface of the tongue. The total time taken for complete dissolution of film will be recorded in seconds and listed by subject.

6.3.5 Prior and Concomitant Medications and Therapies

The World Health Organization Drug Enhanced (WHO DDE) Version Jun2016, format B2 will be used to classify all medications reported during the study to an Anatomical Therapeutic Chemical (ATC) Level 1 term and a standardized medication name.

Prior medication is any medication/therapy stopped prior to the study drug administration, regardless of medication start date. Concomitant medication is any medication started and not stopped before the study drug administration.

Concomitant Medications will be summarized by Anatomical Therapeutic Chemical (ATC) category Level 1 and by standardized medication name. ATC Level 1 categories and standardized medication names will appear in an alphabetical order on the summary table. For each medication, the number of subjects and percentages will be displayed.

The use of prior and/or concomitant medication will be listed by subject.

6.3.6 Medical Histories

Medical history will be collected at screening and reviewed for any exclusionary criteria. The Medical Dictionary for Regulatory Activities (MedDRA®) Version 19.1 will be used to classify all medical history findings to a System Organ Class (SOC) and Preferred Term (PT).

All medical history data will be listed and sorted by subject and alphabetically according to SOC and PT

6.4 Efficacy Analysis

No efficacy analysis is planned as per the protocol. This is a single dose safety study with no measurement of efficacy.

6.5 Safety Analysis

Safety data will be evaluated through the assessment of PAS scores on the VFSS, adverse events (AEs), clinical signs and symptoms from physical and neurological examination following study drug administration, and vital signs assessments. Treatment-Emergent Adverse Events (TEAEs), and vital signs, will be summarized. No inferential analysis will be carried out for the safety data.

Shells for all tables and listing referred to in this section are displayed in separate document.

6.5.1 Adverse Events

Treatment-emergent AE (TEAE)s will be defined as AEs that occur on or after the date and time of study drug administration, or those that first occur pre-dose but worsen in frequency or severity after study drug administration. TEAEs will be captured through the end of the study. TEAEs and non-TEAEs (those occurring prior to administration of study medication or that first occurred prior to study drug administration and did not worsen in frequency or severity) will be listed.

The MedDRA® dictionary version 19.1 will be used to classify all AEs reported during the study by SOC and PT.

The relationship of TEAEs to study drug will be classified according to the study protocol as unrelated, unlikely, possible, or probable. The severity of AEs will be rated according to the study protocol as: mild, moderate, or severe.

An SAE is any untoward medical occurrence that:

- results in death,

- is life-threatening,

- requires inpatient hospitalization or prolongation of existing hospitalization,

- results in persistent or significant disability/incapacity,

- is a congenital anomaly/birth defect

A significant AE will be defined as any event (other than those reported as serious) that necessitated an intervention, including withdrawal of treatment, or significant additional concomitant therapy.

Serious and significant AEs will be listed separately.

6.5.2 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.

Physical and neurological examination data will be listed separately by subject.

Any abnormal findings judged to be clinically significant will be documented as medical history or as an AE, depending upon whether noted at screening, prior to dosing or after dosing, as appropriate. Any physical examination or neurological examination findings documented as AEs will be included in the AE summaries.

6.5.3 Vital Signs

Complete vital sign measurements (blood pressure, heart rate, respiratory rate and temperature) will be performed at screening, and at Visit 1 pre-VFSS 1. The abbreviated vital sign measurements (blood pressure, heart rate, and respiratory rate) will be performed at Visit 1 post-VFSS 2.

Descriptive statistics (sample size, mean, median, SD, Min and Max,) for each vital sign parameter will be presented for screening, pre-VFSS 1, and post-VFSS 2. Unscheduled timepoints will be included in the listings but not in the summary tables except for baseline calculation if applicable. Descriptive statistics for change from baseline for post-VFSS 2 will also be presented. Baseline will be defined as the last non-missing result (scheduled or unscheduled) obtained prior to study drug administration. Results from post-dose repeat tests will not be included in the summary statistics unless the repeat was required (and documented as such) due to technical reasons or an invalid initial result.

A listing of all vital signs results will be provided.

6.5.4 Laboratory Parameters

Clinical laboratory (hematology, serum chemistry, and urinalysis) results will be obtained at screening and at early termination or end of study (post-VFSS 2).

Serum chemistry parameters include the following: alanine aminotransferase (ALT), albumin, aspartate aminotransferase (AST), urea, chloride, creatinine, creatinine kinase, potassium, sodium, bicarbonate, magnesium, bilirubin, and serum pregnancy test.

Hematology parameters include the following: hematocrit, hemoglobin, platelet count, red blood cell count, red blood cell indices (mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC]), neutrophils, lymphocytes, monocytes, eosinophils, basophils, and white blood cell count with differential.

Urinalysis parameters include the following: color and clarity, pH, specific gravity, protein, glucose, ketones, bilirubin, occult blood, nitrite, urobilinogen, leukocytes, and urine pregnancy test. Unless otherwise specified, microscopic examination will be performed on abnormal finding.

Listings of all clinical laboratory results will be provided with the abnormal values flagged with "L" for low and "H" for high for continuous parameters, and “A” for abnormal for categorical parameters.

6.5.5 ALS Functional Rating Scale – Revised (ALSFRS-R)

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 performed at screening, and at Visit 1 pre-VFSS 1. All 12 activities are relevant in ALS.

Descriptive statistics (sample size, median, Min and Max,) will be presented for screening, and at Visit 1 pre-VFSS 1 as appropriate.

A listing of ALSFRS-R results will also be provided, as an overall score, as individual question scores, and by individual functional domains.

6.5.6 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), and will be administered at Screening, and at Visit 1 pre-VFSS 1.

Number and percentage of subjects will be presented for each point on the scale for screening, and for Visit 1 pre-VFSS 1 as appropriate.

A listing of FOIS results will also be provided.

6.5.7 Eating Assessment Tool 10 – (EAT-10)

The Eating Assessment Tool-10, is a validated 10-item patient report scale of perceived swallowing impairment, and will be administered at Screening, and at Visit 1 pre-VFSS 1. 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).

Descriptive statistics (sample size, median, Min and Max,) will be presented for screening, and for Visit 1 pre-VFSS 1 as appropriate.

A listing of EAT-10 results will also be provided.

6.5.8 Statistical Analyses

The primary objective is to assess the effect of the ROSF formulation, if any, of a single 50 mg dose of ROSF on swallowing safety in subjects with ALS. The analyses will be descriptive only, and not hypothesis-testing.

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 and across subjects.

Swallowing Evaluation Results:
There is considerable discussion in the literature regarding the psychometric properties and optimal/correct ways to analyze PAS scores (an 8-point ordinal scale, where higher scores indicate lower function, measured individually for 11 swallowing trials). There is no method universally accepted as best due to the psychometric and clinical characteristics of the PAS. The three methods described below will be used to present the results of this study. This approach was determined *post hoc*, at the time of examining results for the first seven patients.

"Single worst score" method:
A number of publications use the single worst score on any swallowing trial as an indicator of PAS swallowing function. Results presented will include the number/percentage of patients who stay the same, increase or decrease (and by how many points).

"Sum of scores" method:
The sum of 11 PAS scores will be used. Results presented will include the number/percentage of patients who stay the same, increase or decrease sum (and by how much).

"Steele 4-category" method:
Steele and associates (Dysphagia 2017) propose categorization of single worst PAS score into 4 categories. Steele A includes scores 1, 2, 4; Steele B includes 3, 5, 6; Steele C includes a score

of 7 and Steele D includes a worst score of 8. Results presented will include the number/percentage of patients who stay the same, increase or decrease (and by how much).

Interim Analyses:

An unofficial interim analysis was performed after 7 patients had completed the study. As previously mentioned, these results were discussed with the FDA and they agreed with the Sponsor that the study should be terminated after the two additional patients who had been screened but not yet completed were evaluated with the VFSS.

6.6 Changes to Methods Planned in the Protocol

See previous sections regarding methods changed since the protocol.

Based upon FDA feedback Exclusion criteria #2 will be updated to the following:

Subjects with a prior swallowing study that has shown a PAS score of 4 or greater and subjects with a PAS score of 3 or greater and who have exceeded more than 2 abnormal swallows (PAS of 3 or greater) will be excluded from participation in the study.

Videofluoroscopic Swallowing Study (VFSS1 - PAS):

The 12th bolus was inadvertently included as part of the PAS evaluation. This bolus is typically included only to determine if the subject can open the mouth to the diameter of the pill. The PAS is not normally assessed during this bolus; therefore, the 12th bolus trial presentation at the end of the list will be removed from the study and the section 10.2.2. in protocol is clarified as follows:

After consent has been verified and screens completed, the patient will be seated and will complete a standardized bolus protocol that includes 11 bolus trial presentations.

7. REFERENCES

1. Chuang-Stein C. Summarizing laboratory data with different reference ranges in multi-center clinical trials. Drug Information Journal. 1992; 26:77-84.
2. Karvanen J. The statistical basis of laboratory data normalization. Drug Information Journal. 2003; 37:101-107.