CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	212640
Link to EDR	\\CDSESUB1\evsprod\NDA212640\0001
Submission Date	1/31/2019
Submission Type	Original NDA – 505 (b)(2)
Product Name	Exservan® (Riluzole)
Dosage Form and Strength	Oral soluble film, 50 mg
Proposed Dose/Regimen	50 mg twice daily To be taken at least 1 hour before or 2 hours after a meal
Proposed Indication	Treatment of Amyotrophic Lateral Sclerosis (ALS)
Applicant	Aquestive Therapeutics
OCP Division	Division of Clinical Pharmacology I
Associated IND	130939
OCP Review Team	Gopichand Gottipati Ph.D., Sreedharan Sabarinath Ph.D.

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1. Executive Summary

Aquestive Therapeutics submitted an original New Drug Application (NDA 212640) for EXSERVAN® for the treatment of Amyotrophic Lateral Sclerosis (ALS) via 505(b)(2) regulatory pathway. The proposed product is 50 mg oral soluble film. The listed drug is riluzole oral tablet (RILUTEK®) approved in the US in 1996.

This application relies on a pivotal relative bioavailability and food effect study (162020) conducted in healthy subjects to demonstrate a pharmacokinetic (PK) bridge between the proposed product (EXSERVAN® oral soluble film 50 mg) and the listed drug (RILUTEK® oral tablet 50 mg). In this single-dose study, the proposed product was administered without water and listed drug was administered with water, both under fasting conditions. The exposure metrics AUC and Cmax met bioequivalence criteria, therefore EXSERVAN® is bioequivalent to RILUTEK®. RILUTEK® has a food effect (administration of high fat meal decreased AUC by 20% and Cmax by 45% respectively), and therefore, it is required to administer RILUTEK® at least one hour before or two hours after a meal[1]. EXSERVAN® also had similar food effect. Administration of high-fat meal with EXSERVAN® decreased AUC by 15% and Cmax by 45% respectively. Therefore, EXSERVAN® should also be administered one hour before or two hours after a meal, like the listed drug. The relative bioavailability and food effect study conducted by the applicant provides an adequate scientific bridge for this 505(b)(2) application. Therefore, EXSERVAN® can rely on RILUTEK® and borrow information from its approved label.

The Office of Study Integrity and Surveillance (OSIS) was consulted for clinical and analytical site inspections for the pivotal relative bioavailability study 162020. OSIS conducted inspection for the clinical site and found the data are reliable to support a regulatory decision (DARRTS 10/04/2019) and analytical site was previously inspected (DARRTS 04/29/2019). The NDA also included a pilot phase 1 PK study (1897) evaluating BA/BE and organoleptic effect.

2. Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in the NDA and recommends approval based on the bioequivalence demonstrated between 50 mg EXSERVAN® oral soluble film and listed drug RILUTEK® oral tablet 50 mg.

Since EXSERVAN® has food effects similar to that with the listed drug, EXSERVAN® should be taken at least one hour before or two hours after a meal, similar to the listed drug.

[1] USPI of Rilutek 50 mg tablets: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020599s017lbl.pdf

3. Background and Regulatory History

The applicant is seeking approval for EXSERVAN® via 505(b)(2) pathway and are relying on FDA's findings of safety and efficacy of riluzole in addition to the results from the pivotal PK bridging study.

The original clinical development plan (summarized in Table 1 & Table 2) included two phase 1 studies: one pilot BA/BE organoleptic study (1897), and one pivotal relative bioavailability and food effect study (162020); and two phase 2 studies in subjects with ALS: swallowing study 17MO1R-0012 and the long Term (LT) safety study 17MO1R-0016.

In the pre-NDA meeting (dated March 2018), the adequacy of revised clinical development plan and overall submission package for EXSERVAN® was discussed. Upon review of adverse events reported in clinical study report for 162020, apart from oral hypoesthesia and erythema, the agency noted that no other concerning findings of oral cavity irritation were found. Therefore, the agency waived the conduct of study 17MO1R-0016 to assess chronic oral cavity irritation. The swallowing study 17MO1R-0012 was terminated early based on agreement with the agency.

Table 1 Summary of Phase 1 Studies in Clinical Development Plan

Study No.	Study Design	Number of Subjects	Age Range	Dosage and Dosage Regimen	Primary Endpoints
1897	Pilot, open-label, randomized, single-dose, 3-period, 4-arm, crossover, comparative bioavailability study under fasting conditions in healthy volunteers Subjects randomized to receive dosing sequence ABD, CAB, BDC, or DCA	16 enrolled 16 completed: 5 male 11 female[a]	22-59 y	A=1 x 50 mg ROSF without water B=1 x 50 mg ROSF + 240 mL water C=1 x 50 mg Rilutek + 240 mL water D=1 x 50 mg Rilutek crushed with 15 mL applesauce 7-day washout between dosing periods	AUC_t AUC_{inf} C_{max} T_{max} λ $T_{1/2}$ AUC_t/AUC_{inf} Organoleptic effect (tongue, buccal surfaces, hard palate, soft palate, and pharynx) Safety and tolerability
162020	Pivotal, open-label, randomized, single dose, five-period, replicate, crossover, comparative bioavailability study under fasting conditions in healthy volunteers Subjects randomized to receive ABABC and BABAC.	32 enrolled 30 completed	18-64 y	A=1 x 50 mg ROSF without water under fasting conditions B=1 x 50 mg Rilutek + 240 mL of water under fasting conditions C=1 x 50 mg ROSF without water following a standardized high-fat meal 7-day washout between dosing periods	AUC_t AUC_{inf} C_{max} T_{max} K_{el} $T_{1/2}$ Cl/F V_d/F

AUC_t = area under the concentration-time curve from time 0 to time t (ln transformed); AUC_{inf} = area under the concentration-time curve from time 0 to infinity; C_{max} = maximum (peak) plasma drug concentration; ROSF = Riluzole Oral Soluble Film; λ = terminal elimination rate constant; $T_{1/2}$ = elimination half-life.
[a] One subject withdrew at period 2 check-in and returned back for period 3.

Source: Investigational Brochurev2.0: Table – 4 on Page 19

Table 2: Summary of Phase 2 Studies in Clinical Development Plan

Type of Study	Study Identifier	Study Objective	Study Design	Test Products; Dosage Form/Regimen; Route of Administration	No. of Subjects (Gender, Age)	Duration of Treatment	Study Status; Type of Report; Location of Report
Phase 2 Safety	17M01R-0012	**Primary:** Swallowing Safety and Tolerability	Open-label, single-center, single-dose, safety and tolerability study	**Test:** ROF 50 mg Dosage Form: Oral Film Route: Oral **Regimen:** ROF 50mg single dose administered orally	**Subjects with ALS** Enrolled = 9 Completed = 9 **Gender:** Male = 3 Female = 6 **Age:** 18-80 Years	1 Visit	Completed (Terminated early based on agreement with FDA) CSR Section 5.3.1.1
Phase 2 Long-term Safety	17M01R-0016	**Primary:** Safety and Tolerability	Open-label, multi-center, single treatment, safety and tolerability study	**Test:** ROF- 50 mg Dosage Form: Oral Film Route: Oral **Regimen:** ROF 50mg administered orally, twice daily for 12 weeks	**Subjects with ALS** Proposed Enrollment = approx. 25 Enrolled = 0 Completed = 0 **Age:** 18-80 Years	12 weeks of twice-daily treatment (Proposed)	**Terminated prior to enrollment.** No Study Report Protocol located in Section 5.3.1.1

Source: Synopses of Individual Studies Table on Page 4

4. Summary of Pivotal Relative BA/BE and Food Effect Study

Title: A pivotal, open-label, randomized, single dose, five-period, replicate crossover, comparative bioavailability study of EXSERVAN® 50 mg Oral Soluble Film (OSF) and RILUTEK® 50 mg tablet in healthy male and female volunteers under fasting conditions with evaluation of food effect.

Primary Objectives:

- To evaluate the comparative bioavailability of riluzole from EXSERVAN® administered orally as 1 x 50 mg OSF without water under fasting conditions versus RILUTEK® 1 x 50 mg tablets administered orally with 240 ml of water under fasting conditions in healthy non-smoking volunteers.
- To evaluate the food effect on the PK of ROSF, administered as 1 x 50 mg without water following a standardized high-fat meal.

Treatment Administration:

Test and reference products are summarized in Table 3 below.

Table 3 Summary of treatments and instructions for administration

Treatment	Treatment A	Treatment B	Treatment C
Product Administered	EXSERVAN® oral soluble film	RILUTEK® oral tablets	EXSERVAN® oral soluble film
Dose/Strength	50 mg	50 mg	50 mg
Route of administration	Oral, without water, fasting conditions. Film was placed directly on the top of tongue, subject was asked to rub the film gently with the tongue against the roof of the mouth to promote melting and disappearance of the film	Oral, with 240 mL of water	Oral, without water, within 30 min of ingestion of standardized high-fat meal. Similar instructions as treatment A.

Methodology:

Part I of the study compared the PK of the test and reference product in a replicate crossover design, each subject repeated treatments A and B for the assessment of BE under fasting conditions (Periods 1 – 4).

Each subject then received treatment C under fed conditions (standardized high-fat meal) (Period 5)

Sequence	Period 1	Period 2	Period 3	Period 4	Period 5
1	A	B	A	B	C
2	B	A	B	A	C

Part II of the study evaluated the food effect on PK of riluzole with the test product.

Subjects who met the eligibility criteria were randomly assigned equally into one of the 2 treatment sequences with the medications: EXSERVAN® 50 mg under fasting conditions without water (Treatment A), RILUTEK® 50 mg tablet with 240 mL of water under fasting conditions (Treatment B) for part I of the study and EXSERVAN® 50 mg under fed conditions (standardized high-fat meal) without water for part II of the study. There was a washout period of a minimum of 7 days between each period.

PK Sampling:

Blood samples from each subject were drawn into blood collection tubes (3 mL) containing K2 EDTA prior to drug administration (pre-dose) and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, and 120 hours after dosing in each study period.

Number of Subjects (Planned and Analyzed)

A total of 135 healthy subjects were screened for the study, and 45 subjects were enrolled. Of these 45 subjects, 32, 31, 30, 30 and 30 subjects were enrolled in Periods 1, 2, 3, 4 and 5 respectively (Table 4). All subjects who received at least one dose of study medication comprised of safety population (N=32). Of these, 30 subjects completed all treatment periods, 2 subjects discontinued from the study.

Reviewer Comments

The study design, treatment assignment, washout period (7 days, given the half-life of 12 hours), PK sampling scheme and sample size are acceptable

Table 4 Subject disposition characteristics

Category	Riluzole 50 mg Oral Soluble Film Fasting Conditions (A)	RILUTEK® 50 mg Tablet Fasting Conditions (B)	Riluzole 50 mg Oral Soluble Film Fed Conditions (C)	Overall
Screened	-	-	-	135
Screening Failures[1,2]	-	-	-	65 (48.1)
Not Enrolled[1,3]	-	-	-	25 (18.5)
Enrolled[1,4]	-	-	-	45 (33.3)
Dosed in Period 1:	16	16	-	32
Not Dosed:	0	0	-	-
Completed[5]:	16 (100)	16 (100)	-	-
Dosed in Period 2:	16	15	-	31
Not Dosed:	0	1	-	-
Completed[5]:	16 (100)	15 (100)	-	-
Dosed in Period 3:	14	16	-	30
Not Dosed:	2	0	-	-
Completed[5]:	14 (100)	16 (100)	-	-
Dosed in Period 4:	16	14	-	30
Not Dosed:	0	2	-	-
Completed[5]:	16 (100)	14 (100)	-	-
Dosed in Period 5:	-	-	30	30
Not Dosed:	-	-	2	-
Completed[5]:	-	-	30 (100)	-
Completed All Treatment Periods[6]:	-	-	-	30 (93.8)

[1]Percentage based on the number of screened subjects. [2]Screening failures include volunteers who did not meet project criteria

[3]Not enrolled include volunteers who were judged eligible but decided not to participate in study or who were not selected to participate in the study since there was already a sufficient number of subjects.

[4]Enrolled include volunteers who were judged eligible and accepted to participate in the trial after having signed the approved final version of the study informed consent form and also those identified as standby who may replace subjects who withdraw from the study before dosing.

[5]Percentage based on the number of dosed subjects for a given treatment.

[6]Percentage based on the overall number of subjects dosed (safety population)

[7]Includes subjects who discontinued during the washout period or during the baseline assessment; these subjects are included under the last treatment received prior to discontinuation.

[8]Overall, each subject could only contribute once to each reason for discontinuation, regardless of the number of occurrences.

[9]Percentage based on the number of discontinued subjects per treatment group or overall, as appropriate.

Source: Clinical study report (162020) Table 10.1-1, Page 57

Main Criteria for Inclusion and Exclusion

The key inclusion criteria are healthy, male or female subjects, non-smokers (for at least 6 months prior to first drug administration), 18 to 64 years of age (inclusive) with a body mass index (BMI) within 18.5 – 29.9 kg/m^2 (inclusive).

The key exclusion criteria were presence of mouth jewelry, dentures, braces, piercings, or irritation in the mouth or tongue, that in the opinion of the investigator, would likely interfere with successful completion of dosing, known history of clinically significant medical history, concurrent diseases, use of any central nervous system depressants or cytochrome P450 enzyme-modifying drugs (inhibitors, inducers) in the previous 30 days before the first drug administration and subjects having difficulty with swallowing intact tablets or keeping oral soluble films in the mouth until dissolution.

Criteria for Evaluation

Criteria for Relative Bioavailability Assessment

Data from first 4 fasting periods were included in this analysis. The analysis method recommended in FDA draft guidance on progesterone[2] was adapted to reflect the multi-group nature of the study. Briefly, within-subject coefficient of variation was first calculated for the reference product (CV_{WR}). Based on a cut-off value of 30% for CV_{WR} (equivalent to the within-subject standard deviation [SWR] <0.294), the following decision criteria for BE assessment were used:

- *Average BE*: If CV_{WR} < 30% for the primary parameter (AUC_{0-t}, AUC_{0-inf}, and C_{max}), the point estimates and 90% confidence interval (C.I) for the Test-to-Reference geometric mean ratio (A/B) were calculated. If the 90% C.I. for the ratio based on least-square means from the analysis of variance (ANOVA) of ln-transformed parameter(s) is(/are) within 80.00 to 125.00 %, then the test product was concluded to be BE to the reference product for that parameter(s).
- *Scaled-Average BE*: If CV_{WR} ≥ 30% for the primary parameter (AUC_{0-t}, AUC_{0-inf}, and C_{max}), then:
    - The point estimate of the Test-to-Reference should be within 80.00 to 125.00 %, and
    - The 95% upper confidence bound for the scaled average BE criterion should be equal to or less than zero (≤ 0),

    Then the test product was concluded to be BE to the reference product for that parameter(s).

[2] FDA Draft Guidance on Progesterone, Recommended Apr. 2010, Revised Feb 2011. Available online at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatorInformation/Guidances/UCM209294.pdf

Criteria for Determination of Food-Effect

The ratio and 90% C.I. for Fed-Fasted ratio (C/A) were calculated and if the 90% C.I. for the ratio based on the least square means from ANOVA of ln-transformed for AUC_{0-t}, AUC_{0-inf}, and C_{max} are within 80.00 to 125.00%, then it was concluded that there was no food-effect.

The primary PK endpoints were observed C_{max} and $AUC_{0-inf,}$ both derived using non-compartment methods. Other parameters included: AUC_{0-t} and T_{max}.

Reviewer Comments:

The inclusion/exclusion criteria and the criteria for assessing BE (including the decision criteria of using average BE or scaled-average BE method based on CV_{WR} cut-off of 30%[3]) and food-effect are acceptable.

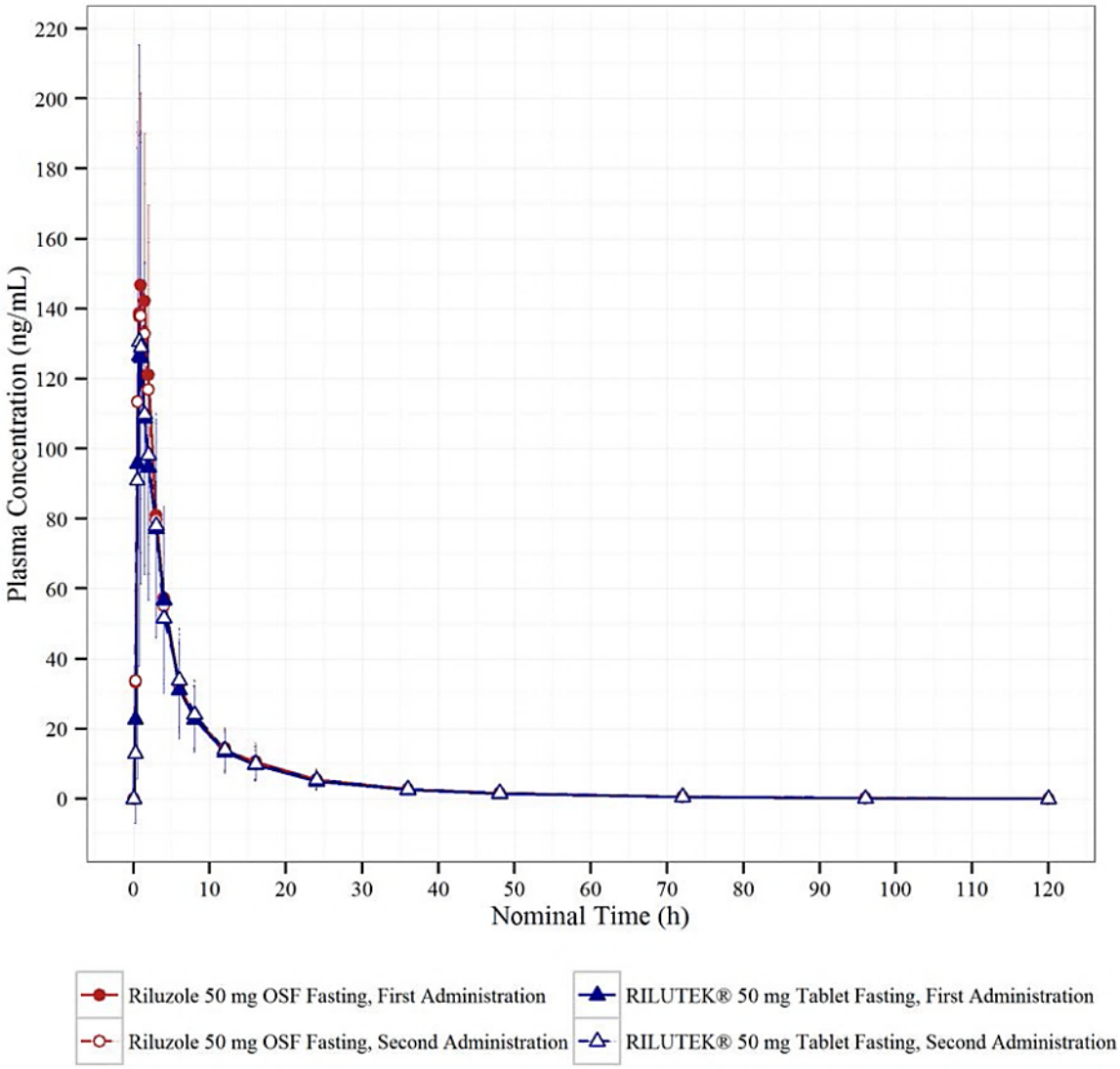
Results

Part I: Bioequivalence Assessment in Fasted State: Test (A) versus Reference (B)

The plot for the mean (±SD) riluzole plasma concentrations over the sampling period are presented in Figure 1 below and the descriptive statistics for PK parameters of the reference product, including CV_{WR} are shown in Table 5. The CV_{WR} values were > 30% for C_{max} alone and ≤ 30% for AUC_{0-inf} and AUC_{0-t}. Therefore, average BE criteria for AUC_{0-inf} and AUC_{0-t}: 90% C.I. for the geometric mean ratio of Test-to-Reference (A/B) were within 80 – 125%; and average scaled-BE criteria were used for C_{max} as described above: the point estimate for Test-to-Reference were be within 80 – 125%, and the 95% upper confidence bound was less than zero (-0.0123). These results are shown in Table 6 below

[3] Davit BM, Chen ML, Conner DP, Haidar SH, Kim S, Lee CH, Lionberger RA, Makhlouf FT, Nwakama PE, Patel DT, Schuirmann DJ. Implementation of a reference-scaled average bioequivalence approach for highly variable generic drug products by the US Food and Drug Administration. The AAPS journal. 2012 Dec 1;14(4):915-24.

Figure 1 Mean (±SD) Riluzole Plasma Concentration (Treatments A and B)



Source: Clinical study report (162020) Figure 11.4.2.3-1, Page 67

Table 5 Summary of Pharmacokinetic Parameters for Riluzole Following RILUTEK® 50 mg Treatment - PK Population

Parameter (units)	RILUTEK® 50 mg Tablet Fasting Conditions (B) (First Administration)				RILUTEK® 50 mg Tablet Fasting Conditions (B) (Second Administration)			
	N	Mean	SD	CV%	N	Mean	SD	CV%
AUC_{0-t} (ng*h/mL)	31	746.62	274.36	36.75	30	768.07	276.05	35.94
AUC_{0-inf} (ng*h/mL)	31	761.08	275.92	36.25	30	784.43	278.53	35.51
Residual Area (%)	31	2.06	0.74	35.78	30	2.23	0.71	31.59
C_{max} (ng/mL)	31	157.32	72.92	46.35	30	148.23	54.94	37.07
$T_{½\ el}$ (h)	31	13.56	4.09	30.15	30	14.99	4.83	32.24
Correlation	31	-0.9901	0.0083	-	30	-0.9878	0.0112	-
K_{el} (/h)	31	0.0556	0.0161	28.8746	30	0.0501	0.0132	26.2674
V_d/F (L)	31	1371.44	419.30	30.57	30	1468.23	431.72	29.40
V_d/F^a(L/kg)	31	19.09	5.41	28.36	30	20.46	5.79	28.31
Cl/F(L/h)	31	74.76	27.30	36.52	30	72.55	27.50	37.91
Cl/F^a(L/(h*kg))	31	1.03	0.33	32.13	30	1.01	0.35	35.20
	N	Median	Min	Max	N	Median	Min	Max
T_{max} (h)	31	0.996	0.499	4.000	30	0.750	0.498	6.000

Source: Clinical study report (162020) Table 11.4.2.3-2, Page 69

Table 6 Ratio of A/B, Confidence Intervals and BE Analysis for PK Parameters – PK Population

Parameter	CV_{WR}	Geometric LSM (A)	Geometric LSM (B)	Ratio[1]	90% Geometric C.I.[2] Lower	90% Geometric C.I.[2] Upper	95% upper confidence bound[2]
AUC_{0-t} (ng*h/mL)	12.65%	780.01	714.48	109.17%	105.67%	112.79%	-
AUC_{0-inf} (ng*h/mL)	12.49%	795.98	730.02	109.04%	105.58%	112.61%	-
C_{max} (ng/mL)	32.66%	-	-	115.82%	-	-	-0.0123

[1] Point estimate of the geometric mean ratio (A/B).
[2] Reference-scaled average bioequivalence approach.
LSM: Least-squares mean

Source: Clinical study report (162020) Table 11.4.2.3-4, Page 71

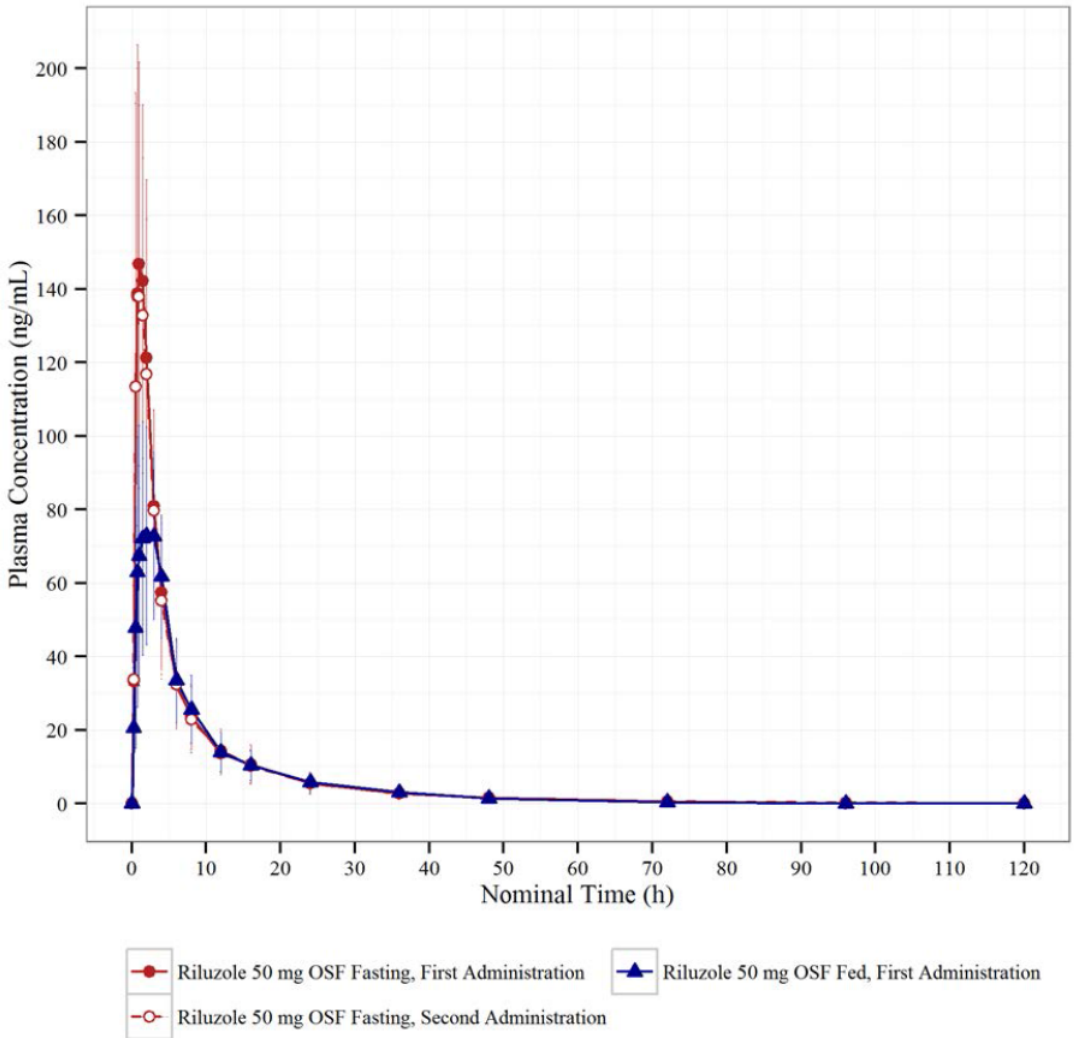
Reviewer Comments

The reviewer was able to replicate the analyses conducted by the applicant. The results indicate that the test and reference products show similar rate and extent of riluzole absorption after single dose administration under fasting conditions.

Part II: Food Effect Assessment

The plot for the mean (±SD) riluzole plasma concentrations over the sampling period are presented for the test product without (treatment A) and with standardized high-fat meal (treatment C) in Figure 2 below

Figure 2 Mean (±SD) Riluzole Plasma Concentration (Treatments A and C)



Source: Clinical study report (162020) Figure 11.4.2.3-2, Page 72

The results for geometric mean ratios for fed/fasted with 90% CI are shown in Table 7 below: C_{max} decreased by 45%, while $AUC_{0\text{-}inf}$ decreased by 15%.

Table 7 Geometric Mean Ratio (C/A) and 90% Confidence Interval for PK parameters: PK Population

Parameter	Treatment Comparison	Geometric LSM (C)	Geometric LSM (A)	Ratio[1]	90% Geometric C.I.[2] Lower	Upper
$AUC_{0\text{-}t}$ (ng*h/mL)	ROSF 50 mg Fed (C) - ROSF 50 mg Fasting (A)	669.79	779.39	85.94%	82.91%	89.08%
$AUC_{0\text{-}inf}$ (ng*h/mL)	ROSF 50 mg Fed (C) - ROSF 50 mg Fasting (A)	679.35	795.44	85.40%	82.53%	88.38%
C_{max} (ng/mL)	ROSF 50 mg Fed (C) - ROSF 50 mg Fasting (A)	90.34	165.47	54.59%	50.38%	59.16%

[1] Calculated using least-squares means according to the formula: $e^{(Difference)}$ X 100.
[2] 90% Geometric Confidence Interval using ln-transformed data.
LSM: Least-squares mean

Source: Clinical study report (162020) Table 11.4.2.3-6, Page 74

Reviewer Comments

The reviewer was able to replicate the analyses conducted by the applicant. The results indicate that the test product has a significant food effect: C_{max} decreased by 45%, while $AUC_{0\text{-}inf}$ decreased by 15%. The magnitude of the food-effect is consistent with that observed with listed drug (RILUTEK® 50 mg tablet) – decrease of C_{max} by 45% and AUC by 20%. The USPI for RILUTEK® includes a recommendation: should be taken at least 1 hour before or 2 hours after a meal. Therefore, an identical recommendation should be included in the USPI of EXSERVAN®.

5. Bioanalytical Method Validation

A validated HPLC method using MS/MS detection was employed for determining the concentrations of riluzole in human plasma. The sample analysis was conducted in accordance with the FDA Guidance for the Industry, Bioanalytical Method Validation (May 2018) and EMA Guideline on Bioanalytical Method Validation. The validation method included the assessment of linearity, precision, accuracy, dilution and recovery, matrix effect, selectivity, carry-over and stability

This method involved the extraction of riluzole and the internal standard riluzole-^{13}C-$^{15}N_2$ from human EDTA K2 plasma using an automated protein precipitation procedure and LC-MS/MS determination according to method SOP (b) (4) 10942.01. Samples were kept frozen at -20ºC prior to analysis and 0.05 mL of matrix was used for analysis. Bioanalytical methods and validation results are summarized in Table 8.

Reviewer Comments

The method was shown to be precise, accurate, sensitive, and selective over the validated range. Furthermore, the method was reliable and reproducible, and the analyte and the internal standard were stable under all conditions tested. Based on these results, the method was considered suitable for the analyses for riluzole in human plasma over the range of 0.50 to 500 ng/mL.

Table 8 Summary of Bioanalytical Method and Validation Characteristics

Parameter	Parent Drug
Analyte	Riluzole
Internal Standard (IS)	Riluzole-^{13}C-$^{15}N_2$
Limit of quantification (ng/ml)	Lower Limit of Quantification (LLOQ): 0.5
Average recovery of drug (%)	Means: 87.72, 95.26, 92.71
Average recovery of IS (%)	Mean: 95.55
Calibration curve range (ng/mL) and linearity (r^2)	0.5 to 500 ng/mL; Linearity: $r^2 \geq 0.9957$
QC concentrations (ng/mL)	LLQC: 0.5, QC1: 1.5, QC2: 250 and QC3: 375
Between-run accuracy and precision	Biases: -2.03 to 4.38%; CV: 1.92 to 10.79%
Within-run accuracy and precision	Biases: -4.70 to 6.00%; CV: 0.82 to 7.15%
Bench-top stability (hrs) (equivalent to short-term stability of analyte in matrix)	24h 05min at room temperature; 25h 07min at 4°C
Stock stability (days) (equivalent to long-term stability of analyte or internal standard in solution)	729 days at -20°C (low and high concentrations)
Processed stability (hrs) (equivalent to post-preparative stability)	95h 47min at room temperature
Freeze-thaw stability (cycles)	4 cycles at -20°C and -80°C
Long-term storage stability (days) (equivalent to long-term stability of analyte in matrix)	731 days at -20°C
Selectivity	No effect on the quantitation of the analyte

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