CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209080Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA Number:	NDA 209080
Submission Type:	Original NDA - 505(b)(2)
Applicant Name:	DJA Global Pharmaceuticals, Inc.
Submission Dates:	11/16/2017
Brand Name:	TIGLUTIK™
Generic Name	Riluzole
Dosage Form:	Oral Suspension
Dosage Strength:	5mg/mL
Proposed Dose:	50 mg (10 mL), taken orally every 12 hrs
Proposed Indication:	Treatment of amyotrophic lateral sclerosis (ALS)
Associated IND:	123532
OCP Division:	DCP1
Primary Reviewer:	Bilal AbuAsal, Ph.D.
Team Leader:	Sreedharan Sabarinath, Ph.D.

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

DJA Global Pharmaceuticals, Inc. has submitted an original NDA 209080 for TIGLUTIK™ for the treatment of amyotrophic lateral sclerosis (ALS), through 505(b)(2) regulatory pathway. The reference listed drug, riluzole oral tablet (RILUTEK®) was approved in the US for this indication in 1996. The proposed product, TIGLUTIK™, is a 5 mg/mL oral suspension of riluzole. TIGLUTIK™ is approved and marketed using the tradename TEGLUTIK® in several countries outside the United States (US).

The basis for this 505(b)(2) application is a pivotal relative bioavailability study DSC 15-2985-04 in healthy subjects. This study was conducted to demonstrate a PK bridge for the safety and efficacy of the proposed riluzole oral suspension to US-sourced Rilutek® oral tablets, the reference listed drug (RLD). This single dose study, demonstrated bioequivalence between TIGLUTIK™ oral suspension (50 mg/10 mL) and the RLD (50 mg tablet) under fasting condition. The RLD, riluzole tablet has significant food effects and requires administration at least one hour before or two hours after a meal[1]. Therefore, a food effect arm was included in the pivotal PK bridging study to address the potential food effect of riluzole oral suspension. Following the administration of riluzole oral suspension with a high-fat meal, the peak plasma concentration (Cmax) decreased by approximately 55%, while the AUC was not significantly affected (decreased by about 9%).

A consult for site inspection for the pivotal PK bridging study DSC 15-2985-04 was sent to the Office of Study Integrity and Surveillance (OSIS). OSIS recommended accepting data without an on-site inspection because this site was recently inspected and the outcome from the inspection was classified as No Action Indicated (NAI).

The Applicant also submitted three additional PK studies (Studies DSC 15-2985-01, DSC 15-2985-02, DSC 15-2985-03), that were used for the registration of this product in Europe. These studies are not essential and considered as supportive for this NDA.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the information submitted in the NDA and recommends approval based on the bioequivalence demonstrated between the proposed oral suspension and the reference listed drug.

Based on the observed food effect with the oral suspension, we recommend that TIGLUTIK™ should be taken at least 1 hour before or 2 hours after a meal. This dosing instruction is the same as for the reference listed drug (RILUTEK® tablets).

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

2 BACKGROUND AND REGULATORY HISTORY

Riluzole is a glutamate antagonist approved for the treatment of amyotrophic lateral sclerosis. Riluzole was approved in 1996 as a film-coated tablet (RILUTEK®). The recommended dosage for RILUTEK® is 50 mg taken orally twice daily. RILUTEK® should be taken at least 1 hour before or 2 hours after a meal.

The applicant is seeking approval through the 505(b)(2) regulatory pathway and is relying on the FDA's findings on safety and efficacy for RILUTEK® and on the data from the relative bioavailability study DSC 15-2985-04 for establishing a PK bridge between the oral suspension TIGLUTIK® to the reference listed drug (RLD) RILUTEK® tablets.

3 STUDY DSC15-2985-04 AND KEY CLINICAL PHARMACOLOGY FINDINGS

Study Title:

A Phase I, open-Label, pharmacokinetic comparison of riluzole 50 mg/10 mL oral Suspension vs. RILUTEK 50 mg tablet and an estimation of the food-effect on riluzole 50 mg/10 mL oral suspension after single dose in healthy volunteers.

Methodology:

This was a Phase I, single-center, open-label, single-dose, randomized, 3-period, 6-sequence, crossover, comparative bioavailability study, performed under fasting or fed conditions. Prior to study commencement, subjects were randomized to receive a single-dose of study medication; either the test (under fasting or fed conditions) or the reference formulation, in accordance with the randomization scheme. Subjects were confined to the clinical facility from at least 11 hours prior to drug administration until after the 24-hour post-dose blood draw, in each period. There were washout periods of seven days between doses.

Blood Sampling Points

Blood samples were collected prior to drug administration and 0.083, 0.167, 0.250, 0.500, 0.750, 1.00, 1.25, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, and 24.0 hours post-dose, in each period.

Number of Subjects (planned and analyzed):

Number of subjects enrolled and randomized: 36

Number of subjects included in the data set for pharmacokinetic (PK) analysis: 34

Diagnosis and Main Criteria for Inclusion:

Subjects had to be healthy, adult non-smokers, aged ≥ 18 and ≤ 55 years, with body mass index (BMI) >18.5 and <30.0 kg/m2, and body weight ≥50.0 kg for males and ≥45.0 kg for females.

Test and Reference Products:

Treatment		
	Test	**Reference**
Product	Tiglutik™	Rilutek®
Treatment Code	A (Fasted) and C (Fed)	B
Strength	5 mg/mL	50 mg
Dosage form	Oral suspension	Film-coated tablet
Dose administered	1 x 10 mL (50 mg)	1 x 50 mg
Route	Oral	Oral
Manufacturer	(b) (4)	Covis Pharmaceuticals Inc., USA

Criteria for Relative Bioavailability/Bioequivalence Assessment

The 90% geometric confidence intervals of the ratio (A/B) of least-squares means from the ANOVA of the ln-transformed AUC0-t, AUC0-inf, and Cmax must be within 80% to 125%.

Criteria for Determination of Food-Effect

No food effect for riluzole 50 mg/10 mL oral suspension was assumed if the 90% geometric confidence intervals of the ratio (C/A) of least-squares means from the ANOVA of the ln-transformed AUC0-t, AUC0-inf, and Cmax were within 80% to 125%.

The primary PK endpoints were (AUC0-inf) and the observed maximum concentration (Cmax), both derived using noncompartmental methods. Other PK parameters included: AUC0-t and AUC0-24 and Tmax.

Comparison of the log-transformed PK parameters Cmax and AUC0-inf and AUC0-t and AUC0-24 across treatments was performed using an analysis of variance (ANOVA) model. The ANOVA model included sequence, treatment, and period as fixed effects and subject within a sequence as a random effect. The ratios of the geometric means (Test/Reference) and 90% confidence intervals (CIs) were reported.

Conclusions were based on the ratio of the geometric means (Test/Reference) and the 90% CI about the ratio. Bioequivalence was concluded if the 90% CIs for the ratio of the geometric means for the AUC0-inf and Cmax fell within the 80% to 125% boundary.

Results:

Evaluation of for Relative Bioavailability/Bioequivalence:

In the assessment of relative bioavailability of riluzole 50 mg/10 mL Oral Suspension and RILUTEK® as 50 mg film-coated tablet in fasting conditions, the test/reference ratio (A/B) of geometric means for AUC0-t, AUC0-inf, and for Cmax were approximately 95% and 108%, respectively, indicating a similar extent and rate of riluzole absorption after single dose of test

and reference formulations. The bioequivalence test was satisfied for all primary endpoints (AUC0-t, AUC0-inf, and Cmax) with the 90% geometric confidence intervals (CI) for the ratio (A/B) of means within the acceptance limits of 80% to 125% (Table 1). The plots of the mean plasma concentration-time profiles are presented in Figure 1.

Table 1. Statistical Summary of the Comparative Bioavailability Data for Bioequivalence Studies (Study DSC/15/2985/04)

Parameter	Treatment Comparisons	Geometric LS Mean (A)	Geometric LS Mean (B)	Ratio[1]	90% Geometric C.I.[2] Lower	90% Geometric C.I.[2] Upper	Intra-Subject CV	Inter-Subject CV
AUC_{0-t}	Test(A) - Reference(B)	570722.85	601508.53	94.88%	90.15%	99.86%	12.48%	48.48%
AUC_{0-inf}	Test(A) - Reference(B)	621227.10	657540.08	94.48%	90.03%	99.15%	11.76%	48.94%
C_{max}	Test(A) - Reference(B)	153322.99	142055.49	107.93%	95.06%	122.54%	31.60%	39.98%
		Geometric LS Mean (C)	Geometric LS Mean (A)					
AUC_{0-t}	Test(C) - Test(A)	521146.78	570644.67	91.33%	87.58%	95.23%	10.19%	42.51%
AUC_{0-inf}	Test(C) - Test(A)	578946.88	621031.45	93.22%	89.30%	97.32%	10.48%	43.69%
C_{max}	Test(C) - Test(A)	70485.55	153397.06	45.95%	42.10%	50.15%	21.50%	36.43%

[1] Calculated using least-squares means according to the formula: $e^{(DIFFERENCE)} \times 100$.

[2] 90% Geometric Confidence Interval using ln-transformed data.

Data source: Tables 14.2.1-9, 14.2.1-10, 14.2.1-11, 14.2.1-12, 14.2.1-13, and 14.2.1-14.

Source: Clinical study report DSC/15/2985/04. Table 11.4.2.3-3, Page 54 of 264. Link: \\cdsesub1\evsprod\nda209080\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\dsc15298504\dsc15298504-report-body.pdf

Evaluation of Food Effect:

Study DSC 15-2985-04 included a food effect arm to address the FDA's inquiry regarding potential food effect of riluzole oral suspension. Following the administration of riluzole 50 mg/10 mL oral suspension (total dose of 50 mg) to healthy subjects under fed conditions with a high-fat meal, Cmax decreases by approximately 55%, while the AUC is not significantly affected by food (decreased by about 9 %). As detailed in the approved RILUTEK® label, a high fat meal decreases absorption, reducing AUC by about 20% and (b) (4) by about 45%. However, the administration of riluzole oral suspension with a high fat meal did not decrease absorption to the same extent (i.e. AUC is not significantly affected by high fat meal). (b) (4)

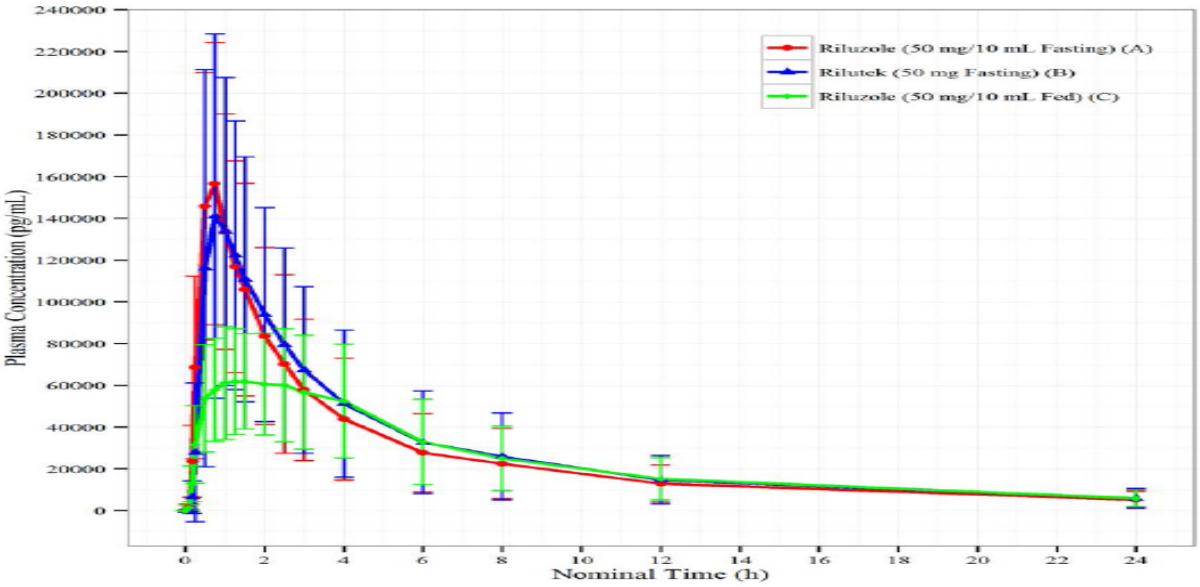
(b) (4)

(b) (4)

(b) (4)

(b) (4) Therefore, we consider having the same dosing instructions for the oral suspension as with the RLD would be appropriate.

Figure 1Mean (±SD) Riluzole Plasma Concentration for each Treatment (N = 34) – Study DSC/15/2985/04



Source: Clinical study report DSC/15/2985/04. Figure 11.4.2.3-1, Page 54 of 264. Link: \\cdsesub1\evsprod\nda209080\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\dsc15298504\dsc15298504-report-body.pdf

Supportive Studies:

The applicant submitted three other clinical PK studies to support the application. These were utilized for the registration of TIGLUTIK in Europe. Two of them were pilot studies (Study DSC/08/2985/01; Study DSC/08/2985/02) and one pivotal study (Study DSC/08/2985/03). All these studies used European sourced reference products.

Study DSC/08/2985/01:

In this pilot study performed in 10 male and female subjects aged 18-55 years, riluzole bioavailability was similar after single 50 mg dose administration of the riluzole 50 mg/10 mL oral suspension (test) and of RILUTEK® 50 mg tablets (reference), as indicated by the 90% CIs of the test/reference ratio of geometric means (i.e., 91.8 to 116.5% and 89.7 to 114.6% for AUC0-t and AUC0-inf, respectively), which fell within the acceptance limits of 80% to 125% specified by the current bioequivalence guidelines. However, on average, a faster riluzole absorption,

characterized by an earlier Tmax and a higher Cmax, was observed with the test as compared to reference formulation (test/reference ratio for the geometric means for riluzole Cmax was 145.3% [90% CIs: 111.2 to 189.8%]).

Study DSC/08/2985/02:

Study DSC/09/2985/02 utilized a randomized, 2-sequence, 4-period, replicate crossover design. Fourteen male and female subjects, aged 18-55 years, were included and received test and reference treatment under fasting conditions in 4 subsequent periods, with a washout period of 7 days between consecutive administrations. Results of the study showed that the geometric mean ratio for AUC0-t and AUC0-inf approached 100%, indicating a similar extent of riluzole exposure after replicate single dose of test and reference formulations. However, Cmax did not meet the BE acceptance criteria. The geometric mean ratio was 116.3% and the 90% CI was (99-137%) The study also showed that Riluzole doesn't have a high intra-individual variability.

Study DSC/09/2985/03:

A total of 30 healthy subjects (15 males, 15 females) were randomized into this single-center, single-dose, 2-period crossover study. Subjects received a single oral dose of 50 mg riluzole as oral suspension (test) and film-coated tablet (reference) under fasting conditions in 2 sequential periods with a 5-day washout period between periods.

The test/reference geometric mean ratio for AUC0-t and AUC0-inf was approximately 107.0%, indicating a similar extent of riluzole absorption after single dose of test and reference formulations. Bioequivalence was demonstrated for both riluzole AUC0-t and AUC0-inf with the 90% CIs of PE% within the acceptance limits of 80% to 125%. The oral suspension showed a slightly higher Cmax than the tablet. The geometric mean ratio for Cmax was around 122.3%, however the 90% CIs for Cmax exceeded the upper limit of the 80% to 125% range specified by the current guidelines for bioequivalence studies (Table 2). This study was accepted for the registration of this product in Europe. It was noticed that However, the mean estimates for Cmax and AUC in this study were about 2-fold different from the reported PK parameters for RILUTEK®. An information request was sent to the sponsor to justify the discrepancy in PK values. The applicant ascribed the discordance in PK parameters (AUC and Cmax) for riluzole between Study DSC/15/2985/04 and Study DSC/09/2985/03 to either the different sources of RILUTEK or the different analytical methods used in the two studies.

Table 2 Main riluzole PK parameters after single oral administration of 50 mg riluzole test and reference formulations, and results of bioequivalence testing. N. of subjects=30

Parameter	Test	Reference	PE%*	90%CI
C_{max} (ng/mL)	393.67±208.02	321.12±163.49	122.32%	103.28 – 144.88%
AUC_{0-t} (ng/mL×h)	1189.74±516.98	1138.66±483.42	106.84%	96.98 – 117.71%
$AUC_{0-\infty}$ (ng/mL×h)	1297.37±573.26	1250.59±557.25	106.46%	96.68 – 117.23%
T_{max} (h)	0.50 (0.25–2.00)	0.75 (0.50-2.00)	NA	NA
$t_{½}$ (h)	8.02±1.64	8.11±1.40	NA	NA

*Values are arithmetic means ± SD, except for T_{max}: median (range); *Point estimate: ratio of geometric means; NA: Not applicable; Source: Table 14.2.2.1, Table 14.2.2.2 and Table 14.2.3.1*

Source: Clinical study report (DSC 15-2985-03), Table 13.1.1, page 55 of 103. Link: \\cdsesub1\evsprod\nda209080\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\dsc09298503\dsc09298503-report-body.pdf

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 FDA Guidance for Industry, Bioanalytical Method Validation (May 2001) and EMA Guideline on Bioanalytical Method Validation. The validation method included the assessment of linearity, precision, accuracy, dilution, recovery, matrix effect, selectivity, carry-over, and stability.

This method involves the extraction of riluzole and the internal standard (riluzole-^{13}C,$^{15}N_2$) from human plasma using an automated protein precipitation procedure and LC-MS/MS determination. Samples were kept frozen at -20ºC prior to analysis and 0.050 mL of matrix was used for analysis.

The method was shown to be precise, accurate, sensitive, and selective over the validated ranges. The method was reliable and reproducible and the analytes and the internal standards were stable under all conditions tested. The method is considered suitable for the analyses of riluzole in human plasma over the range of 0.5 to 500 pg/mL. The bioanalytical method validation is summarized in Table 3.

Table 3 Study DSC/15/2985/04 – Bioanalytical Method Validation

Parameter	**Value**
Bioanalytical method validation report location	16-2-5-3-validation-report Analyte
Analyte	Riluzole
Internal standard (IS)	Riluzole-^{13}C, $^{15}N2$
Limit of quantitation (pg/mL)	500
Average recovery of drug (%)	102, 98, 95
Average recovery of IS (%)	98

Standard curve concentrations (pg/mL)	0.5, 1, 10, 50, 100, 200, 400, 500
QC concentrations (pg/mL)	LLQC: 0.5, QC1: 15, QC2: 250, QC3: 375
QC Intraday precision range (%)	0.85 to 6.69
QC Intraday accuracy range (%)	-1.60 to 1.38
QC Interday precision range (%)	1.83 to 4.96
QC Interday accuracy range (%)	-0.27 to 1.36
Bench-top stability (hrs) (equivalent to short-term stability of analyte in matrix)	23 hours and 10 minutes at 4°C 22 hours and 08 minutes at 4°C (fortified with Riluzole N-Glucuronide)
Stock stability (days) (equivalent to long-term stability of analyte or internal standard in solution)	Riluzole: 82 days at -20ºC Riluzole-13C,15N2: 82 days at -20ºC
Processed stability (hrs) (equivalent to post-preparative stability)	145 hours and 58 minutes at room temperature 121 hours and 41 minutes at room temperature
Freeze-thaw stability (cycles)	4 cycles at -20°C 4 cycles at -20°C
Long-term storage stability (days) (equivalent to long-term stability of analyte in matrix)	133 days at -20°C 132 days at -20°C
Selectivity	No interfering peaks noted in blank plasma samples for analyte and its internal standard.

4 SUMMARY AND CONCLUSION

The applicant submitted four clinical PK studies to compare the pharmacokinetics of riluzole from TIGLUTIK™ oral suspension and the reference product RILUTEK® tablets. The bioequivalence study DSC 15-2985-03 along with two pilot studies (Study DSC/08/2985/01 and Study DSC/08/2985/02) that used European sourced reference standards supported the registration of this product in Europe. Study DSC 15-2985-04 is the pivotal study that supports the current NDA.

Study DSC 15-2985-04 demonstrated that TIGLUTIK™ oral suspension is bioequivalent to RILUTEK® for both AUC and Cmax. We consider the observed food effect with TIGLUTIK™ similar to that observed with the RLD. Therefore, the dosing instructions of TIGLUTK™ should be same as that of the RLD (i.e., should be taken at least 1 hour before or 2 hours after a meal).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BILAL S ABU ASAL
07/17/2018

SREEDHARAN N SABARINATH
07/18/2018