CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-599/S002

Trade Name: Rilutek, 50 mg tablets

Generic Name: riluzole

Sponsor: Aventis Pharmaceuticals

Approval Date: May 19, 2003

Indications: Treatment of patients with amyotrophic lateral sclerosis (ALS)

CENTER FOR DRUG EVALUATION AND RESEARCH

NDA 20-599/S002

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-599/S002

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-599/S-002/S-003/S-005

Aventis Pharmaceuticals
Attention: Kerry Rothschild, J.D.
Director, Regulatory Affairs
200 Crossing Boulevard, P.O. Box 6890
Bridgewater, NJ 08807-0890

Dear Mr. Rothschild:

Please refer to your supplemental new drug applications dated December 24, 1996 (S-002), December 22, 1998 (S-003), and August 17, 1999 (S-005) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rilutek (riluzole) 50 mg tablets.

We acknowledge receipt of your submission dated April 24, 2003. Your submission of April 24, 2003, constituted a complete response to our September 6, 2000, and December 18, 2002 action letters.

These "Prior Approval" supplemental new drug applications propose the following revisions to product labeling:

S-002
This supplement provides for revisions to the **CLINICAL PHARMACOLOGY-Pharmacokinetics-Special Populations** subsection to describe the special population effects of age, renal impairment and hepatic impairment on the tolerability and pharmacokinetics of riluzole.

S-003
This supplement provides for revisions to the **CLINICAL PHARMACOLOGY-Pharmacokinetics-Special Populations** subsection to revise the statement which indicates a difference in clearance between Japanese and Caucasian subjects.

S-005
This supplement provides for revisions to the **PRECAUTIONS-Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection based upon the results of two carcinogenicity studies.

Additionally, we note that you have incorporated our requested revisions to labeling, as communicated in our September 6, 2000, and December 18, 2002 action letters, verbatim.

We have completed the review of these supplemental applications, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (Label Code: 50069093). Accordingly, these supplemental applications are approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions regarding this letter, call Paul David, R.Ph., Senior Regulatory Project Manager, at (301) 594-5530.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
5/19/03 01:49:00 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-599/S002

OTHER ACTION LETTERS

Food and Drug Administration
Rockville MD 20857

NDA 20-599/S-002 & 003

Aventis Pharmaceutical Products Inc.
Attention: Ronald F. Panner
500 Arcola Road
P.O. Box 5096
Collegeville, PA 19426-0800

SEP 6 2000

Dear Mr. Panner:

Please refer to your supplemental new drug application dated December 24, 1996 (SLR-002) and December 22, 1998 (SLR-003), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rilutek ® (riluzole) Tablets.

We acknowledge receipt of the following submissions:

September 23, 1996 November 4, 1998 May 9, 2000

S-002 provided for updated pharmacokinetic data in patients with chronic liver and renal insufficiency and pharmacokinetic data with respect to age and gender. S-003 provides for a re-analysis of comparative pharmacokinetics in Japanese and Caucasian subjects.

We have completed the review of these applications, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit draft labeling revised as follows:

CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations

1. Hepatic Impairment: Your proposed label changes are acceptable, however, please revise the proposed sentence according to the following minor changes (number of subjects and severity of liver impairment included):

   "The area-under-the-curve (AUC) of riluzole, after a single 50 mg oral dose increases by about 1.7-fold in patients with mild chronic liver insufficiency (n= 6; Child - Pugh's score A) and by about 3-fold in patients with moderate chronic liver insufficiency (n= 6; Child - Pugh's score B) compared to healthy volunteers (n= 12) (see WARNINGS and PRECAUTIONS)."

2. Renal Impairment: Your proposed label changes are acceptable, however, please revise the proposed sentence according to the following minor changes (number of subjects included):

   "There is no significant difference in pharmacokinetic parameters between patients with moderate (n= 5; creatinine clearance 30-50 $ml.min^{-1}$) and severe (n= 7; creatinine clearance < 30 $ml.min^{-1}$) renal insufficiency and healthy volunteers (n= 12) after a single oral dose of 50 mg riluzole."

In addition the following statements should be included in the Special Populations sections under CLINICAL PHARMACOLOGY, Pharmacokinetics, and PRECAUTIONS.

a)" The pharmacokinetics of riluzole has not been studied in patients undergoing hemodialysis."

b) "The pharmacokinetics of riluzole has not been studied in patients with severe hepatic impairment."

3. Age: All proposed label changes are acceptable.

4. Gender: The proposed label changes are acceptable with the exception of the following minor change:

"However, in one placebo-controlled clinical trial with population pharmacokinetics, riluzole mean clearance was found to be 30% (b) (4) lower in female patients (corresponding to an approximate increase in AUC of 45% (b) (4)) as compared to male patients."

5. Smoking: The proposed label changes should be replaced by the following sentences:

"Patients who smoke cigarettes eliminate riluzole 20% (b) (4) faster than non-smoking patients, based on a population pharmacokinetic analysis on data from 128 ALS patients, of whom 19 were smokers. However, there is no need for dosage adjustment in these patients."

The review of the population pharmacokinetic (PPK) analysis resulted in a lower estimation of the effect of smoking on clearance than what the sponsor had determined. The following comments regarding the PPK analysis are for informational purposes only, no response is requested:

a) The assumption of the use of the same variance estimate to the several distributions in the inter-occasion variability model was not properly justified. A more general model applied by the FDA led to the convergence with a better objective function value and similar variabilities on all parameters. Moreover, the 95% confidence intervals calculated for the additional parameters (smoking and gender influences on clearance) were less skewed for the FDA model and included zero value for the smoking factor. Therefore, the parameter estimates obtained with the FDA model are considered to be more reliable.

b) You adequately performed the covariate analysis with evaluation of demographic factors, laboratory data, kidney and liver status, gender and smoking status. Clearance values were significantly influenced by gender. A typical male patient had 30% higher clearance than a typical female patient. The influence of smoking was statistically significant; however, the FDA model estimated this influence as 20% and sponsor's model as 36%. This modest increase in clearance values does not warrant

dose adjustment in this population. In the studied population of 128 ALS patients, there were only 19 smokers.

6. Race: The proposed label changes for this section should not be implemented with the exception of the following:

   PRECAUTIONS, Special populations, 2nd sentence. Please keep the following, slightly altered, statement: "Also, female patients and Japanese patients may possess a lower metabolic capacity to eliminate riluzole compared to males and Caucasian subjects, respectively (see CLINICAL PHARMACOLOGY: Special populations).

   The reason for keeping the unrevised (currently approved) text regarding race is as follows: The explanation submitted to us to only use single dose data for a comparison between Japanese and Caucasian subjects shows some discrepancy with the remainder of the data submitted for the label changes. Steady state data would be more reliable for the analysis, especially in light of the improved bioanalytical method, where the limit of quantitation (LOQ) has been lowered from 5 ng/mL (used in Studies 157 and 158) to 0.5 ng/mL. The reported t½ for normal healthy volunteers after a single dose (Studies 164 and 165) was on average 24-30 hours using the more sensitive bioanalytical method (LOQ 0.5 ng/mL), whereas it was calculated to be 5-6 h for both Japanese and Caucasian subjects (LOQ 5 ng/mL). The calculations of total $AUC_{(0\text{-}inf)}$ will be underestimated by using a much shorter t½. Therefore, steady state data using the AUC calculated for one dosing interval should be a much more reliable estimate. In the statistical analysis submitted in 1998, the steady state $AUC_{(0\text{-}12h,Day\ 13)}$ normalized for both weight and dose, was statistically significantly different between the two populations.

   Unfortunately, we were not provided with a further explanation about what the inconsistencies in the steady state data (Day 13) are between the Japanese and Caucasian subjects that would make any comparison at steady state potentially unreliable.

   In the original NDA review, concerns regarding the metabolic data from the two studies were raised. According to the original review the two populations also showed dissimilarities in metabolic patterns: "In both Japanese and Caucasian subjects, <2% of unchanged riluzole is recovered in the urine. However, in Japanese subjects only 15-20% of the administered dose is recovered in the urine as a major glucuronide metabolite as compared to about 40% in Caucasians. This would suggest some differences in the qualitative and quantitative role of the different metabolic pathways involved in the metabolism of riluzole."

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options

under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Melina Fanari, R.Ph., Regulatory Management Officer, at (301) 594-5526.

Sincerely,

9/6/00

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 20-599
HFD-120/Div. Files
HFD-120/Fanari 8/18/00
HFD-120/Katz/Feeney/Fanari
HFD-860/Sunzel / Baweja / HS 8/17/00
DISTRICT OFFICE 8/17/00

APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-599/S002

LABELING

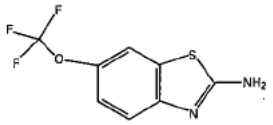
APPROVED
MAY 19 2003

Prescribing Information as of January 2003

RILUTEK®
(riluzole) Tablets
Rx only

DESCRIPTION

RILUTEK® (riluzole) is a member of the benzothiazole class. Chemically, riluzole is 2-amino-6-(trifluoromethoxy)benzothiazole. Its molecular formula is $C_8H_5F_3N_2OS$ and its molecular weight is 234.2. Its structural formula is as follows:



Riluzole is a white to slightly yellow powder that is very soluble in dimethylformamide, dimethylsulfoxide and methanol, freely soluble in dichloromethane, sparingly soluble in 0.1 N HCl and very slightly soluble in water and in 0.1 N NaOH. RILUTEK is available as a capsule-shaped, white, film-coated tablet for oral administration containing 50 mg of riluzole. Each tablet is engraved with "RPR 202" on one side.

Inactive Ingredients: Core: anhydrous dibasic calcium phosphate, USP; microcrystalline cellulose, NF; anhydrous colloidal silica, NF; magnesium stearate, NF; croscarmellose sodium, NF. **Film coating:** hydroxypropyl methylcellulose, USP; polyethylene glycol 6000; titanium dioxide, USP.

CLINICAL PHARMACOLOGY

Mechanism of Action

The etiology and pathogenesis of amyotrophic lateral sclerosis (ALS) are not known, although a number of hypotheses have been advanced. One hypothesis is that motor neurons, made vulnerable through either genetic predisposition or environmental factors, are injured by glutamate. In some cases of familial ALS the enzyme superoxide dismutase has been found to be defective.

The mode of action of RILUTEK is unknown. Its pharmacological properties include the following, some of which may be related to its effect: 1) an inhibitory effect on glutamate release, 2) inactivation of voltage-dependent sodium channels, and 3) ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors.

Riluzole has also been shown, in a single study, to delay median time to death in a transgenic mouse model of ALS. These mice express human superoxide dismutase bearing one of the mutations found in one of the familial forms of human ALS.

It is also neuroprotective in various *in vivo* experimental models of neuronal injury involving excitotoxic mechanisms. In *in vitro* tests, riluzole protected cultured rat motor neurons from the excitotoxic effects of glutamic acid and prevented the death of cortical neurons induced by anoxia.

Due to its blockade of glutamatergic neurotransmission, riluzole also exhibits myorelaxant and sedative properties in animal models at doses of 30 mg/kg (about 20 times the recommended human daily dose) and anticonvulsant properties at a dose of 2.5 mg/kg (about 2 times the recommended human daily dose).

Pharmacokinetics

Riluzole is well-absorbed (approximately 90%), with average absolute oral bioavailability of about 60% (CV=30%). Pharmacokinetics are linear over a dose range of 25 to 100 mg given every 12 hours. 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, mainly to albumin and lipoproteins over the clinical concentration range.

The 50 mg market tablet was equivalent, with respect to AUC, to the tablet used in the dose ranging clinical trials, while the C_{max} was approximately 30% higher. Both tablets have been used in clinical trials. However, if doses greater than those recommended are given, it is likely that higher plasma levels will be achieved, the safety of which has not been established (see DOSAGE AND ADMINISTRATION).

Metabolism and Elimination

Riluzole is extensively metabolized to six major and a number of minor metabolites, not all of which have been identified. Some metabolites appear pharmacologically active in *in vitro* assays. The metabolism of riluzole is mostly hepatic and consists of cytochrome P450-dependent hydroxylation and glucuronidation.

There is marked interindividual variability in the clearance of riluzole, probably attributable to variability of CYP 1A2 activity, the principal isozyme involved in N-hydroxylation.

In vitro studies using liver microsomes show that hydroxylation of the primary amine group producing N-hydroxyriluzole is the main metabolic pathway in human, monkey, dog and rabbit. In humans, cytochrome P450 1A2 is the principal isozyme involved in N-hydroxylation. *In vitro* studies predict that CYP 2D6, CYP 2C19, CYP 3A4 and CYP 2E1 are unlikely to contribute significantly to riluzole metabolism in humans. Whereas direct glucuroconjugation of riluzole (involving the glucurotransferase isoform UGT-HP4) is very slow in human liver microsomes, N-hydroxyriluzole is readily conjugated at the hydroxylamine group resulting in the formation of O- (>90%) and N-glucuronides.

Following a single 150 mg dose of ^{14}C-riluzole to 6 healthy males, 90% and 5% of the radioactivity was recovered in the urine and feces respectively over a period of 7 days. Glucuronides accounted for more than 85% of the metabolites in urine. Only 2% of a riluzole dose was recovered in the urine as unchanged drug.

Special Populations

Hepatic Impairment: The area-under-the-curve (AUC) of riluzole, after a single 50 mg oral dose, increases by about 1.7-fold in patients with mild chronic liver insufficiency (n=6; Child-Pugh's score A) and by about 3-fold in patients with moderate chronic liver insufficiency (n=6; Child-Pugh's score B) compared to healthy volunteers (n=12) (see WARNINGS and PRECAUTIONS). The pharmacokinetics of riluzole have not been studied in patients with severe hepatic impairment.

Renal Impairment: There is no significant difference in pharmacokinetic parameters between patients with moderate (n=5; creatinine clearance 30-50 $ml.min^{-1}$) and severe (n=7; creatinine clearance <30 $ml.min^{-1}$) renal insufficiency and healthy volunteers (n=12) after a single oral dose of 50 mg riluzole. The pharmacokinetics of riluzole have not been studied in patients undergoing hemodialysis.

Age: The pharmacokinetic parameters of riluzole after multiple dose administration (4.5 days of treatment at 50 mg riluzole b.i.d.) are not affected in the elderly (≥ 70 years).

Gender: No gender effect on riluzole pharmacokinetics has been found in young or elderly healthy subjects. However, in one placebo-controlled clinical trial with population pharmacokinetics, riluzole mean clearance was found to be 30% lower in female patients (corresponding to an approximate increase in AUC of 45%) as compared to male patients. No favorable or adverse effects of riluzole in relation to gender were seen in controlled trials, however.

Smoking: Patients who smoke cigarettes eliminate riluzole 20% faster than non-smoking patients, based on a population pharmacokinetic analysis on data from 128 ALS patients, of whom 19 were smokers. However, there is no need for dosage adjustment in these patients.

Race: Clearance of riluzole in Japanese subjects native to Japan was found to be 50% lower as compared to Caucasians after normalizing

for body weight. Although it is not clear if this difference is due to genetic or environmental factors (e.g., smoking, alcohol, coffee, and dietary preferences), it is possible that Japanese subjects may possess a lower capacity (oxidative and/or conjugative) for metabolizing riluzole. There are no studies, however, of lower doses in Japanese subjects (see PRECAUTIONS).

Clinical Trials

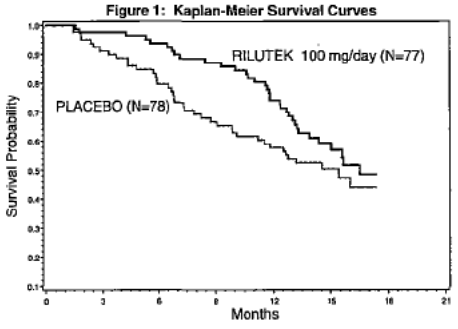
The efficacy of RILUTEK as a treatment of ALS was established in two adequate and well-controlled trials in which the time to tracheostomy or death was longer for patients randomized to RILUTEK than for those randomized to placebo.

These studies admitted patients with either familial or sporadic ALS, a disease duration of less than 5 years, and a baseline forced vital capacity greater than or equal to 60%.

In one study, performed in France and Belgium, 155 ALS patients were followed for at least 13 months (maximum duration 18 months) after being randomized to either 100 mg/day (given 50 mg BID) of RILUTEK or placebo.

Figure 1, which follows, displays the survival curves for time to death or tracheostomy. The vertical axis represents the proportion of individuals alive without tracheostomy at various times following treatment initiation (horizontal axis). Although these survival curves were not statistically significantly different when evaluated by the analysis specified in the study protocol (Logrank test p=0.12), the difference was found to be significant by another appropriate analysis (Wilcoxon test p=0.05). As seen, the study showed an early increase in survival in patients given riluzole. Among the patients in whom treatment failed during the study (tracheostomy or death) there was a difference between the treatment groups in median survival of approximately 90 days. There was no statistically significant difference in mortality at the end of the study.

Figure 1: Kaplan-Meier Survival Curves



In the second study, performed in both Europe and North America, 959 ALS patients were followed for at least 1 year (North American centers) and up to 18 months (European centers) after being randomized to either 50, 100, 200 mg/day of RILUTEK or placebo. Figure 2, which follows, displays the survival curves for time to death or tracheostomy for patients randomized to either 100 mg/day of RILUTEK or placebo. Although these survival curves were not statistically significantly different when evaluated by the analysis specified in the study protocol (Logrank test p = 0.076), the difference was found to be significant by another appropriate analysis (Wilcoxon test p = 0.05). Not displayed in Figure 2 are the results of 50 mg/day of RILUTEK which could not be statistically distinguished from placebo and the results of 200 mg/day which are essentially identical to 100 mg/day. As seen, the study showed an early increase in survival in patients given riluzole. Among the patients in whom treatment failed during the study (tracheostomy or death) there was a difference between the treatment groups in median survival of

50069093
Prescribing Information as of January 2003

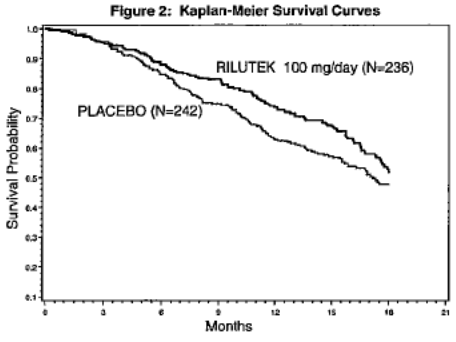
RILUTEK®
riluzole
Tablets

Aventis

RILUTEK®
riluzole
Tablets

approximately 60 days. There was no statistically significant difference in mortality at the end of the study.

Figure 2: Kaplan-Meier Survival Curves



Although riluzole improved early survival in both studies, measures of muscle strength and neurological function did not show a benefit.

INDICATIONS AND USAGE

RILUTEK is indicated for the treatment of patients with amyotrophic lateral sclerosis (ALS). Riluzole extends survival and/or time to tracheostomy.

CONTRAINDICATIONS

RILUTEK is contraindicated in patients who have a history of severe hypersensitivity reactions to riluzole or any of the tablet components.

WARNINGS

Liver Injury / Monitoring Liver Chemistries

RILUTEK should be prescribed with care in patients with current evidence or history of abnormal liver function indicated by significant abnormalities in serum transaminase (ALT/SGPT; AST/SGOT), bilirubin, and/or gamma-glutamate transferase (GGT) levels (see PRECAUTIONS and DOSAGE ADMINISTRATION sections). Baseline elevations of several LFTs (especially elevated bilirubin) should preclude the use of RILUTEK.

RILUTEK, even in patients without a prior history of liver disease, causes serum aminotransferase elevations. Experience in almost 800 ALS patients indicates that about 50% of riluzole-treated patients will experience at least one ALT/SGPT level above the upper limit of normal, about 8% will have elevations > 3 X ULN, and about 2% of patients will have elevations > 5 X ULN. A single non-ALS patient with epilepsy treated with concomitant carbamazepine and phenobarbital experienced marked, rapid elevations of liver enzymes with jaundice (ALT 26 X ULN, AST 17 X ULN, and bilirubin 11 X ULN) four months after starting RILUTEK; these returned to normal 7 weeks after treatment discontinuation.

Maximum increases in serum ALT usually occurred within 3 months after the start of riluzole therapy and were usually transient when < 5 times ULN. In trials, if ALT levels were < 5 times ULN, treatment continued and ALT levels usually returned to below 2 times ULN within 2 to 6 months. Treatment in studies was discontinued, however, if ALT levels exceeded 5 X ULN, so that there is no experience with continued treatment of ALS patients once ALT values exceed 5 times ULN (see PRECAUTIONS: Laboratory Tests). There were rare instances of jaundice.

Liver chemistries should be monitored (see PRECAUTIONS).

Neutropenia

Among approximately 4000 patients given riluzole for ALS, there were three cases of marked neutropenia (absolute neutrophil count less than 500/mm^3), all seen within the first 2 months of riluzole treatment. In one case, neutrophil counts rose on continued treatment. In a second case, counts rose after therapy was stopped. A

third case was more complex, with marked anemia as well as neutropenia and the etiology of both is uncertain. Patients should be warned to report any febrile illness to their physicians. The report of a febrile illness should prompt treating physicians to check white blood cell counts.

PRECAUTIONS

Use in Patients with Concomitant Disease

RILUTEK should be used with caution in patients with concomitant liver insufficiency (see WARNINGS, CLINICAL PHARMACOLOGY). In particular, in cases of RILUTEK-induced hepatic injury manifested by elevated liver enzymes, the effect of the hepatic injury on RILUTEK metabolism is unknown.

Special Populations

Riluzole should be used with caution in elderly patients whose hepatic function may be compromised due to age. Also, female patients and Japanese patients may possess a lower metabolic capacity to eliminate riluzole compared to males and Caucasian subjects, respectively (see CLINICAL PHARMACOLOGY: Special Populations).

Information for the Patient

Patients should be advised to report any febrile illness to their physicians (see WARNINGS: Neutropenia).

Patients and caregivers should be advised that RILUTEK should be taken on a regular basis and at the same time of the day (*e.g.*, in the morning and evening) each day. If a dose is missed, take the next tablet as originally planned (see DOSAGE AND ADMINISTRATION).

Patients should be warned about the potential for dizziness, vertigo, or somnolence and advised not to drive or operate machinery until they have gained sufficient experience on RILUTEK to gauge whether or not it affects their mental and/or motor performance adversely. Whether alcohol increases the risk of serious hepatotoxicity with RILUTEK is unknown; therefore, patients being treated with RILUTEK should be discouraged from drinking excessive amounts of alcohol.

Patients should also be made aware that RILUTEK should be stored at temperatures between 20°-25°C (68°-77°F) and protected from bright light.

RILUTEK must be kept out of the reach of children.

Laboratory Tests

It is recommended that serum aminotransferases including ALT levels be measured before and during riluzole therapy. Serum ALT levels should be evaluated every month during the first 3 months of treatment, every 3 months during the remainder of the first year, and periodically thereafter. Serum ALT levels should be evaluated more frequently in patients who develop elevations (see WARNINGS). As noted in the WARNINGS Section, there is no experience with continued treatment of patients once ALT exceeds 5 X ULN. If a decision is made to continue to treat these patients, frequent monitoring (at least weekly) of complete liver function is recommended. Treatment should be discontinued if ALT exceeds 10 X ULN or if clinical jaundice develops. Because there is no experience with rechallenge of patients who have had RILUTEK discontinued for ALT > 5 X ULN, no recommendations about restarting RILUTEK can be made.

In the two controlled trials in patients with ALS, the frequency with which values for hemoglobin, hematocrit, and erythrocyte counts fell below the lower limit of normal was greater in RILUTEK-treated patients than in placebo-treated patients; however, these changes were mild and transient. The proportions of patients observed with abnormally low values for these parameters showed a dose-response relationship. Only one patient was discontinued from treatment because of severe anemia. The significance of this finding is unknown.

Drug Interactions

There have been no clinical studies designed to evaluate the interaction of riluzole with other drugs.

As with all drugs, the potential for interaction by a variety of mechanisms is a possibility.

Hepatotoxic Drugs: The clinical trials in ALS excluded patients on concomitant medications which were potentially hepatotoxic, (*e.g.*, allopurinol, methyldopa, sulfasalazine). Accordingly, there is no information about the safety of administering RILUTEK in conjunction with such medications. If the practitioner chooses to prescribe such a combination, caution should be exercised.

Drugs Highly Bound To Plasma Proteins: Riluzole is highly bound (96%) to plasma proteins, binding mainly to serum albumin and to lipoproteins. The effect of riluzole (up to 5 mcg/mL) on warfarin (5 mcg/mL) binding did not show any displacement of warfarin. Conversely, riluzole binding was unaffected by the addition of warfarin, digoxin, imipramine and quinine at high therapeutic concentrations.

Effect of Other Drugs On Riluzole Metabolism: *In vitro* studies using human liver microsomal preparations suggest that CYP 1A2 is the principal isozyme involved in the initial oxidative metabolism of riluzole and, therefore, potential interactions may occur when riluzole is given concurrently with agents that affect CYP 1A2 activity. Potential inhibitors of CYP 1A2 (*e.g.*, caffeine, phenacetin, theophylline, amitriptyline, and quinolones) could decrease the rate of riluzole elimination, while inducers of CYP 1A2 (*e.g.*, cigarette smoke, charcoal-broiled food, rifampicin, and omeprazole) could increase the rate of riluzole elimination.

Effect of Riluzole On the Metabolism of Other Drugs: CYP 1A2 is the principal isoenzyme involved in the initial oxidative metabolism of riluzole; potential interactions may occur when riluzole is given concurrently with other agents which are also metabolized primarily by CYP 1A2 (*e.g.*, theophylline, caffeine, and tacrine). Currently, it is not known whether riluzole has any potential for enzyme induction in humans.

Drug Laboratory Test Interactions: None known

Carcinogenesis, Mutagenesis, Impairment of Fertility

Riluzole was not carcinogenic in mice or rats when administered for 2 years at daily oral doses up to 20 mg/kg and 10 mg/kg, respectively, which are approximately equivalent to the maximum human dose on a mg/m^2 basis.

The genotoxic potential of riluzole was evaluated in the bacterial mutagenicity (Ames) test, the mouse lymphoma mutation assay in L5178Y cells, the *in vitro* chromosomal aberration assay in human lymphocytes and the *in vivo* rat cytogenetic assay and *in vivo* mouse micronucleus assay in bone marrow. There was no evidence of mutagenic or clastogenic potential in the Ames test, the mouse lymphoma assay, or the *in vivo* assays in the mouse and rat. There was an equivocal clastogenic response in the *in vitro* lymphocyte chromosomal aberration assay.

Riluzole impaired fertility when administered to male and female rats prior to and during mating at an oral dose of 15 mg/kg or 1.5 times the maximum daily dose on a mg/m^2 basis (see PRECAUTIONS: "Pregnancy" for effects on fertility).

Pregnancy

Pregnancy category C:

Oral administration of riluzole to pregnant animals during the period of organogenesis caused embryotoxicity in rats and rabbits at doses of 27 mg/kg and 60 mg/kg, respectively, or 2.6 and 11.5 times, respectively, the recommended maximum human daily dose on a mg/m^2 basis. Evidence of maternal toxicity was also observed at these doses. When administered to rats prior to and during mating (males and females) and throughout gestation and lactation (females), riluzole produced adverse effects on pregnancy (decreased implantations, increased intrauterine death) and offspring viability and growth at an oral dose of 15 mg/kg or 1.5 times the maximum daily dose on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women. Riluzole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Women

In rat studies, ^{14}C-riluzole was detected in maternal milk. It is not known whether riluzole is excreted in human breast milk. Because many drugs are excreted in human milk, and because the potential for serious adverse reactions in nursing infants from RILUTEK® is unknown, women should be advised not to breast-feed during treatment with RILUTEK.

Geriatric Use

Age-related compromised renal and hepatic function may cause a decrease in clearance of riluzole (see CLINICAL PHARMACOLOGY: Special Populations). In controlled clinical trials, about 30% of patients were over 65. There were no differences in adverse effects between younger and older patients.

Pediatric Use

The safety and the effectiveness of RILUTEK in pediatric patients have not been established.

ADVERSE REACTIONS

The most commonly observed AEs associated with the use of RILUTEK more frequently than placebo treated patients were: asthenia, nausea, dizziness, decreased lung function, diarrhea, abdominal pain, pneumonia, vomiting, vertigo, circumoral paresthesia, anorexia, and somnolence. Asthenia, nausea, dizziness, diarrhea, anorexia, vertigo, somnolence, and circumoral paresthesia were dose related.

Approximately 14% (n = 141) of the 982 individuals with ALS who received RILUTEK in pre-marketing clinical trials discontinued treatment because of an adverse experience. Of those patients who discontinued due to adverse events, the most commonly reported were: nausea, abdominal pain, constipation, and ALT elevations. In a dose response study in ALS patients, the rates of discontinuation of RILUTEK for asthenia, nausea, abdominal pain, and ALT elevation were dose related.

Incidence in Controlled ALS Clinical Studies

Table 1 lists treatment-emergent signs and symptoms that occurred in at least 2% of patients with ALS treated with RILUTEK (n=794) participating in placebo-controlled trials and were numerically greater in the patients treated with RILUTEK 100 mg/day than with placebo or for which a dose response relationship is suggested. The prescriber should be aware that these figures cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and non-drug factors to the AE incidences in the population studied.

Table 1
Adverse Events Occurring in Placebo-Controlled Clinical Trials
†Percentage of patients reporting events

Body System / Adverse Event†	Riluzole 50 mg/day (N=237)	Riluzole 100 mg/day (N=313)	Riluzole 200 mg/day (N=244)	Placebo (N=320)
Body as a Whole				
Asthenia	14.8	19.2	20.1	12.2
Headache	8.0	7.3	7.0	6.6
Abdominal pain	6.8	5.1	7.8	3.8
Back pain	1.7	3.2	4.1	2.5
Aggravation reaction	0.4	1.3	2.0	0.9
Malaise	0.4	0.6	1.2	0.0
Digestive				
Nausea	12.2	16.3	20.5	10.6
Vomiting	4.2	4.2	4.5	1.6
Dyspepsia	2.5	3.8	6.1	5.0
Anorexia	3.8	3.2	8.6	3.8
Diarrhea	5.5	2.9	9.0	3.1
Flatulence	2.5	2.6	2.0	1.9
Stomatitis	0.8	1.0	1.2	0.0
Tooth disorder	0.0	1.0	1.2	0.3
Oral Moniliasis	0.4	0.6	1.2	0.3
Nervous				
Hypertonia	5.9	6.1	5.3	5.9
Depression	4.2	4.5	6.1	5.0
Dizziness	5.1	3.8	12.7	2.5
Dry mouth	3.0	3.5	2.0	3.4
Insomnia	2.1	3.5	2.9	3.4
Somnolence	0.8	1.9	4.1	1.3
Vertigo	2.5	1.9	4.5	0.9
Circumoral paresthesia	1.3	1.6	3.3	0.0
Skin and Appendages				
Pruritus	3.8	3.8	2.5	3.1
Eczema	0.8	1.6	1.6	0.6
Alopecia	0.0	1.0	1.2	0.6
Exfoliative dermatitis	0.0	0.6	1.2	0.0
Respiratory				
Decreased lung function	13.1	10.2	16.0	9.4
Rhinitis	8.9	6.4	7.8	6.3
Increased cough	2.1	2.6	3.7	1.6
Sinusitis	0.4	1.0	1.6	0.9
Cardiovascular				
Hypertension	6.8	5.1	3.3	4.1
Tachycardia	1.3	2.6	2.0	1.3
Phlebitis	0.4	1.0	0.8	0.3
Palpitation	0.4	0.6	1.2	0.9
Postural hypotension	0.8	0.0	1.6	0.6
Metabolic and Nutritional Disorders				
Weight loss	4.6	4.8	3.7	4.7
Peripheral edema	4.2	2.9	3.3	2.2
Musculoskeletal System				
Arthralgia	5.1	3.5	1.6	3.4
Urogenital System				
Urinary tract infection	2.5	2.6	4.5	2.2
Dysuria	0.0	1.0	1.2	0.3

Other Adverse Events Observed
Other events which occurred in more than 2% of patients treated with RILUTEK 100 mg/day but equally or more frequently in the placebo group included: accidental injury, apnea, bronchitis, constipation, death, dysphagia, dyspnea, flu syndrome, heart arrest, increased sputum, pneumonia, and respiratory disorder.

The overall adverse event profile for RILUTEK was similar between females and males, and was independent of age. Because the largest non-white racial subgroup was only 2% of patients exposed to RILUTEK (18/794) in placebo-controlled trials, there are insufficient data to support a statement regarding the distribution of adverse experience reports by race. In ALS studies, dizziness did occur more commonly in females (11%) than in males (4%). There was not a difference between females and males in the rates of discontinuation of RILUTEK for individual adverse experiences.

Other Adverse Events Observed During All Clinical Trials
RILUTEK has been administered to 1713 individuals during all clinical trials, some of which were placebo-controlled. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. The frequencies presented represent the proportion of the 1713 individuals exposed to RILUTEK who experienced an event of the type cited on at least one occasion while receiving RILUTEK. All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; *rare* adverse events are those occurring in fewer than 1/1000 patients.

*** = AE frequency ≤ to placebo**

Body as a Whole: *Frequent:* Hostility*. *Infrequent:* Abscess*, sepsis*, photosensitivity reaction*, cellulitis, face edema*, hernia, peritonitis, attempted suicide, injection site reaction, chills*, flu syndrome, intentional injury, enlarged abdomen, neoplasm. *Rare:* Acrodynia, hypothermia, moniliasis*, rheumatoid arthritis.

Digestive System: *Infrequent:* Increased appetite, intestinal obstruction*, fecal impaction, gastrointestinal hemorrhage, gastrointestinal ulceration, gastritis*, fecal incontinence, jaundice, hepatitis, glossitis, gum hemorrhage*, pancreatitis, tenesmus, esophageal stenosis. *Rare:* Cheilitis*, cholecystitis, hematemesis, melena*, biliary pain, proctitis, pseudomembranous enterocolitis, enlarged salivary gland, tongue discoloration, tooth caries.

Nervous System: *Frequent:* Agitation*, tremor. *Infrequent:* Hallucinations, personality disorder*, abnormal thinking*, coma, paranoid reaction*, manic reaction, ataxia, extrapyramidal syndrome, hypokinesia, urinary retention, emotional lability, delusions, apathy, hypesthesia, incoordination, confusion*, convulsion, leg cramps, amnesia, dysarthria, increased libido, stupor, subdural hematoma, abnormal gait, delirium, depersonalization, facial paralysis, hemiplegia, decreased libido, myoclonus. *Rare:* Abnormal dreams, acute brain syndrome, CNS depression, dementia, cerebral embolism, euphoria*, hypotonia, ileus*, peripheral neuritis, psychosis*, psychotic depression, schizophrenic reaction, trismus, wristdrop.

Skin and Appendages: *Infrequent:* Skin ulceration, urticaria, psoriasis, seborrhea*, skin disorder, fungal dermatitis*. *Rare:* Angioedema, contact dermatitis, erythema multiforme, furunculosis*, skin moniliasis, skin granuloma, skin nodule.

Respiratory System: *Infrequent:* Hiccup, pleural disorder*, asthma, epistaxis, hemoptysis, yawn, hyperventilation*, lung edema*, hypoventilation*, lung carcinoma, hypoxia, laryngitis, pleural effusion, pneumothorax*, respiratory moniliasis, stridor.

Cardiovascular System: *Infrequent:* Syncope*, hypotension, heart failure, migraine, peripheral vascular disease, angina pectoris*, myocardial infarction*, ventricular extrasystoles, cerebral hemorrhage, atrial fibrillation*, bundle branch block, congestive heart failure, pericarditis, lower extremity embolus, myocardial ischemia*, shock*. *Rare:* Bradycardia, cerebral ischemia, hemorrhage, mesenteric artery occlusion, subarachnoid hemorrhage, supraventricular tachycardia*, thrombosis, ventricular fibrillation, ventricular tachycardia.

Metabolic and Nutritional Disorders: *Infrequent:* Gout*, respiratory acidosis, edema, thirst*, hypokalemia, hyponatremia, weight gain*. *Rare:* Generalized edema, hypercalcemia, hypercholesteremia.

Endocrine System: *Infrequent:* Diabetes mellitus, thyroid neoplasia. *Rare:* Diabetes insipidus, parathyroid disorder.

Hemic and Lymphatic System: *Infrequent:* Anemia*, leukocytosis, leukopenia, ecchymosis. *Rare:* Neutropenia, aplastic anemia, cyanosis, hypochromic anemia, iron deficiency anemia, lymphadenopathy, petechiae*, purpura.

Musculoskeletal System: *Infrequent:* Arthrosis, myasthenia*, bone neoplasm. *Rare:* Bone necrosis, osteoporosis, tetany.

Special Senses: *Infrequent:* Amblyopia, ophthalmitis. *Rare:* Blepharitis, cataract, deafness, diplopia*, ear pain, glaucoma, hyperacusis, photophobia, taste loss, vestibular disorder.

Urogenital System: *Infrequent:* Urinary urgency, urine abnormality, urinary incontinence, kidney calculus, hematuria, impotence, prostate carcinoma, kidney pain, metrorrhagia, priapism. *Rare:* Amenorrhea, breast abscess, breast pain, nephritis*, nocturia, pyelonephritis, enlarged uterine fibroids, uterine hemorrhage, vaginal moniliasis.

Laboratory Tests: *Infrequent:* Increased gamma glutamyl transferase, abnormal liver function/tests, increased alkaline phosphatase, positive direct Coombs test, increased gamma globulins. *Rare:* increased lactic dehydrogenase.

OVERDOSAGE
No specific antidote or information on treatment of overdosage with RILUTEK is available. In the event of overdose, RILUTEK therapy should be discontinued immediately. Treatment should be supportive and directed toward alleviating symptoms.

Experience with riluzole overdose in humans is limited. Methemoglobinemia of undetermined origin has been reported in association with a riluzole overdose many times the recommended daily dose. This was rapidly reversible after treatment with methylene blue. The estimated oral median lethal dose is 94 mg/kg and 39 mg/kg for male mice and rats, respectively.

DOSAGE AND ADMINISTRATION
The recommended dose for RILUTEK is 50 mg every 12 hours. No increased benefit can be expected from higher daily doses, but adverse events are increased.

RILUTEK tablets should be taken at least an hour before, or two hours after, a meal to avoid a food-related decrease in bioavailability.

Special Populations
Patients with Impaired Hepatic Function: see WARNINGS, PRECAUTIONS, CLINICAL PHARMACOLOGY.

HOW SUPPLIED
RILUTEK 50 mg tablets are white, film-coated, capsule-shaped and engraved with "RPR 202" on one side. RILUTEK is supplied in bottles of 60 tablets, NDC 0075-7700-60.

STORE AT CONTROLLED ROOM TEMPERATURE 20°-25°C (68°-77°F) AND PROTECT FROM BRIGHT LIGHT.
KEEP OUT OF THE REACH OF CHILDREN.

Manufactured by:
Aventis Pharma (Nenagh) Ltd.
Lisbunny Ind. Estate, Nenagh
Co. Tipperary, Ireland

Manufactured for:
AVENTIS PHARMACEUTICALS PRODUCTS INC.
BRIDGEWATER, NJ 08807 USA

Rev. January 2003

50069093

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-599/S002

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Review of Carcinogenicity Studies

NDA:	20-599
Drug Name:	Rilutek ® (riluzole) (RP54274)
Indication:	ALS
Sponsor:	Aventis
Pharmacologist:	Aisar Atrakchi, Ph.D. (HFD-120)
Date of Document:	March 22, 2000
Dataset Submitted:	March 9, 2001

In this NDA submission two animal carcinogenicity studies, one in mice and one in rats, were included. The objective of these studies was to determine the effect of test article RP54274 (riluzole) on the incidence and morphology of tumors in mice and rats when administered once daily by oral gavage for approximately 2 years at some selected dose level.

The reviewer's analyses are performed using software called "carcin" written by Dr. Ted Guo of CDER/FDA.

1. The Mouse Study (Study 96008)

1.1 Introduction

In this study animals were divided into 5 groups of 50/sex. Animals received the vehicle, 0.5% methylcellulose, (administered to two control groups) or RP54274 at 5, 10 or 20 mg/kg by oral gavage once daily for 104 weeks.

1.2 Sponsor's Results

The number of mice that died or were euthanatized prior to study termination was similar in all groups. In addition, statistical analysis of intercurrent mortality showed no significant differences between mice treated with RP54274 and controls.

There was no statistically significant increase in the incidence of any tumor type for mice treated with RP54274 compared to the combined control groups.

There was no effect of RP54274 on body weight or body weight gain. Mean body weights and body weight gains of the treated males were comparable to the males of the two control groups throughout the study. Mean body weights of the females in the RP54274 treated groups were generally comparable to those of the control groups. However, mean body weights of the 20 mg/kg/day female group were slightly (0.3 to 2.0

grams) less than those of the combined control groups during the last 32 weeks of the study.

The sponsor concluded that RP54274 was not carcinogenic to Crl: CD-1 (ICR) BR mice when administered orally at doses of 5, 10 or 20 mg/kg/day for 2 years.

1.3 Reviewer's Analysis

This reviewer will analyze the survival data with trend tests based on Cox's method and Kruskal-Wallis method, and Kaplan-Meier estimate plots of all treatment groups.

In this mouse study, the Cox trend statistics for comparing proportions alive were not statistically significant for males or females (see "Dose-Mortality Trend Tests" and "Kaplan-Meier Survival Function" in Appendix).

Tumor trends will be evaluated using exact permutation trend tests based on Peto et al. (1980) principles. In this review trends in tumor incidence rates are tested for statistical significance at .025 and .005 for rare (defined as background rate of 1% or less) and common tumors, respectively. These levels of significance ensure despite the multiplicity of testing an overall false positive rate of about 10% in the two-year two-species two-gender bioassay.

In this mouse study, using the level .025 and .005 for rare and common tumors, there were no statistically significant increasing tumor trends for males or females (see "Test for Dose-Tumor Positive Linear Trend" in Appendix).

1.4 Validity of the Study

As there were no statistically significant differences between the high dose groups and the controls in tumors among the male and female mice, the validity of the studies needs to be evaluated. Two questions need to be answered (Haseman (1984)):

(i) Were enough animals exposed for a sufficient length of time to allow for late developing tumors?
(ii) Were the dose levels high enough to pose a reasonable tumor challenge in the animals?

To answer the first question, the following rules of thumb were suggested by experts in the field: Haseman (1985) found that on the average, approximately 50% animals in the high dose group survived a two-year study. Chu et al. (1981) proposed that 'To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one year'.

In this mouse study, more than 80% of the mice in the high dose groups of males and females survived one year, and about 50% survived two years (see "Analysis of Mortality" in Appendix). Based on the suggestions of the above experts, the length of the

exposure and the number of animals surviving for both male and female mice are considered sufficient.

To determine the adequacy of the chosen dose levels, it is generally accepted that the high dose should be close to MTD. Chu et al (1981) suggested:

(i) 'A dose is considered adequate if there is a detectable weight loss of up to 10% in a dosed group relative to the control'.
(ii) 'The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical'.
(iii) 'In addition, doses are considered adequate if the dosed animals show a slightly increased mortality compared to the controls'.

The mean body weights of the combined controls and the high dose males or females were comparable, and did not show a detectable difference. The mortality rates of the high dose groups are comparable to those of the combined control groups, except for males whose rate is higher in the first year. This differential was not maintained during the remainder of the study. Therefore, the MTD does not appear to have been reached. The evaluation of clinical signs and histopathologic toxic effects of the drug is left to the expertise of the reviewing pharmacologist.

2. The Rat Study (Study 95087)

2.1 Introduction

In this study, animals were divided into 5 groups of 65/sex. Animals received either 0.5% (w/v) methylcellulose (2 control groups) or RP54274 at 2, 5 or 10 mg/kg by oral gavage once daily for 101 (males) and 104 (females) weeks.

2.2 Sponsor's Results

The number of rats that died or were euthanatized prior to study termination was similar in all groups. Thus, there was no treatment effect on overall mortality at study termination. However, overall survival of the male mice in the 10 mg/kg/day (high-dose) group was slightly decreased with respect to the control groups from month 11 through month 18 of the study.

There was no statistically significant increase in the incidence of any tumor type in rats treated with RP54274.

Group mean body weights of the males in the 10 mg/kg/day (high-dose) group and 5 mg/kg/day (mid-dose) group were consistently, although slightly (7% or less), lower than the mean weights of males in the combined control groups after the first two weeks of the study, as indicated by the statistically significant ($p \leq .05$) trend in the male average time response analysis. These decreases were typically dose-related. There was also a

significant ($p \leq .05$) difference in the average time response analysis for the males in the 2 mg/kg/day (low-dose) group, although this was not considered biologically meaningful because the effect on body weight was very slight and most of the mean body weight values were in fact very close to the corresponding values of the second control group. Group mean body weights of the females in all treatment groups were generally comparable to control values. The mean body weights of the 10 mg/kg/day (high-dose females) during the last months of the study (days 645-722) were 9 to 13% lower than the corresponding mean weights of the combined control groups, but this was of no toxicological significance because of the biological variability and small sample sizes at the end of the study.

The sponsor concluded that the oral administration of RP54274 to Crl: CD-1 (SD) BR rats at doses of 2, 5 or 10 mg/kg/day for 2 years did not produce any evidence of carcinogenicity.

2.3 Reviewer's Analysis

The same analyses as in Section 1 will be performed for analyzing the rat study.

The rat study was terminated during week 101 for males and 104 for females.

In this rat study, the Cox and Kruskal-Wallis trend statistics for comparing proportions alive were not statistically significant for males or females (see "Dose-Mortality Trend Tests" and "Kaplan-Meier Survival Function" in Appendix).

Using the level .025 and .005 for rare and common tumors, there were no significant increasing tumor trends for males or females (see "Test for Dose-Tumor Positive Linear Trend" in Appendix).

2.4 Validity of the Study

The validity of the rat study is evaluated following the same criteria described in Section 1.4.

In this rat study, more than 80% in the high dose groups of males or females survived one year, about 60% (58.5% for the high dose males) survived one year and half, and about 20% survived two years (see "Analysis of Mortality" in Appendix). This suggests that there was a sufficient length of exposure and a sufficient number of animals to allow for the development of late tumors (see "Analysis of Mortality" in Appendix). Mortality of the high dose males was increased compared to the controls during the first year, but not sustained thereafter.

However, the mean body weight of the high dose males was slightly less than that of the combined controls for most of the study. This suggests that MTD was reached for these animals. For the female rats the criteria for the MTD appear not to have been met.

3. Conclusion

Based on the analysis of the mouse and rat studies, neither dose-mortality trend tests nor tests for positive dose-tumor trend are statistically significant, which confirms the sponsor's results.

In evaluating the validity of the mouse study, it was found that the MTD might not have been reached for the mice, though the survival was considered adequate. For the rat study, both sexes appeared to have a sufficient number of animals living long enough. The high dose appears to have been close to the MTD for the male rats but not the females.

4. Reference

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Kun He, Statistical Reviewer

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Roswitha Kelly, M.S.
Pre-clinical Coordinator

Dr. George Chi, Director

CC: HFD-120/Fanari
HFD-120/Atrakchi
HFD-120/Rosloff
HFD-120/Katz
HFD-710/Kelly
HFD-710/Jin
HFD-710/Chi
HFD-700/Anello

Appendix

1. **Mouse-Male**
   a) Number of Animals
   b) Analysis of Mortality
   c) Dose-Mortality Trend Tests
   d) Kaplan-Meier Survival Function
   e) Test for Dose-Tumor Positive Linear Trend

2. **Mouse-Female**
   f) Number of Animals
   g) Analysis of Mortality
   h) Dose-Mortality Trend Tests
   i) Kaplan-Meier Survival Function
   j) Test for Dose-Tumor Positive Linear Trend

3. **Rat-Male**
   k) Number of Animals
   l) Analysis of Mortality
   m) Dose-Mortality Trend Tests
   n) Kaplan-Meier Survival Function
   o) Test for Dose-Tumor Positive Linear Trend

4. **Rat-Female**
   p) Number of Animals
   q) Analysis of Mortality
   r) Dose-Mortality Trend Tests
   s) Kaplan-Meier Survival Function
   t) Test for Dose-Tumor Positive Linear Trend

Number of Animals
Species: Mouse
Sex: Male

	Treatment Group					
	CTRL1	CTRL2	LOW	MED	HIGH	Total
	N	N	N	N	N	N
Week						
0-52	1	3	4	1	8	17
53-78	9	7	7	8	7	38
79-91	5	7	3	8	2	25
92-102	9	11	6	8	7	41
103-104	26	22	30	25	26	129
Total	50	50	50	50	50	250

Source: C:\CARC2\XAnimalX.txt

Analysis of Mortality
Species: Mouse
Sex: Male

	Dose														
	CTRL1			CTRL2			LOW			MED			HIGH		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
Week															
0-52	1	50	2.0	3	50	6.0	4	50	8.0	1	50	2.0	8	50	16.0
53-78	9	49	20.0	7	47	20.0	7	46	22.0	8	49	18.0	7	42	30.0
79-91	5	40	30.0	7	40	34.0	3	39	28.0	8	41	34.0	2	35	34.0
92-102	9	35	48.0	11	33	56.0	6	36	40.0	8	33	50.0	7	33	48.0
103-104	26	50	52.0	22	50	44.0	30	50	60.0	25	50	50.0	26	50	52.0

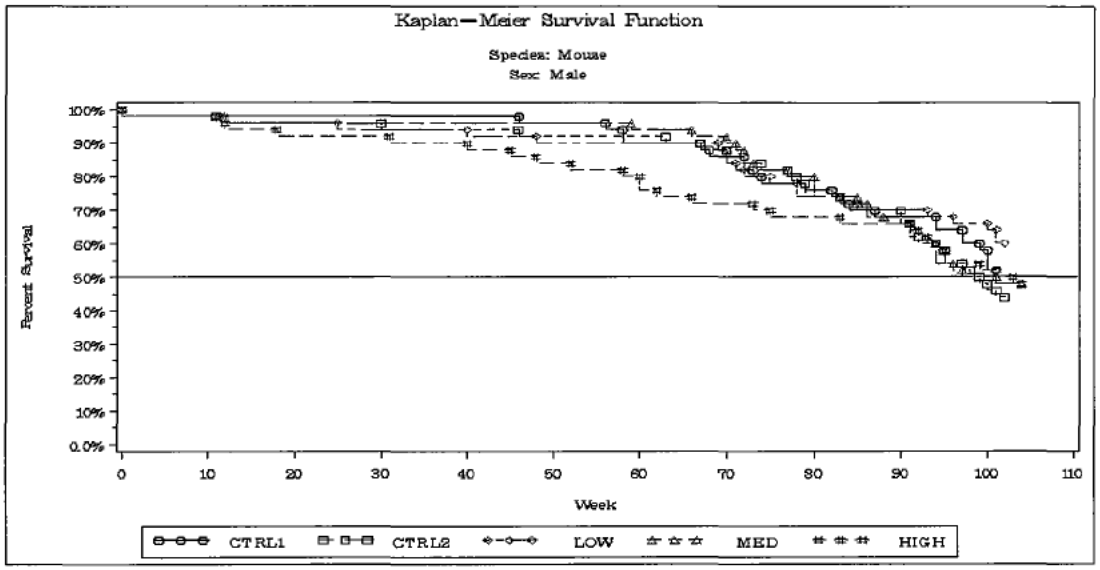
Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Mouse
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.09	0.7666
	Depart from Trend	2.17	0.5376
	Homogeneity	2.26	0.6882
Kruskal-Wallis	Dose-Mortality Trend	0.44	0.5062
	Depart from Trend	1.72	0.6336
	Homogeneity	2.16	0.7069

Source: C:\CARC2\XAnimalX.txt


Kaplan—Meier Survival Function
Species: Mouse
Sex: Male
Percent Survival
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0.0%
0
10
20
30
40
50
60
70
80
90
100
110
Week
CTRL1
CTRL2
LOW
MED
HIGH

Test for Dose-Tumor Positive Linear Trend

Source: Male Mouse Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL 1	CTRL 2	LOW	MED	HIGH	Tumor type	pValue (Exact)	pValue (Asymp)
ADRENAL (2)	ORG001	B-Pheochromocytoma	756	1%	1	0	0	0	0	IN	1.0000	0.8494
ADRENAL (2)	ORG001	B-Spindle cell adenoma	759	2%	2	0	0	0	0	IN	1.0000	0.9223
ADRENAL (2)	ORG001	B-Cortical adenoma	861	1%	1	0	1	1	0	IN	0.7196	0.7118
BRAIN	ORG006	B-Meningioma	381	.0%	0	0	1	0	0	IN	0.6250	0.6391
CECUM	ORG007	M-Carcinoma	372	.0%	0	0	0	1	1	MX	0.1021	0.0548
DUODENUM	ORG009	B-Adenoma	787	.0%	0	0	0	0	1	IN	0.1953	0.0450
EAR	ORG010	B-Mast cell tumor	725	.0%	0	0	1	0	0	IN	0.6279	0.6387
EPIDIDYMIS (2)	ORG011	B-Hemangioma	747	.0%	0	0	0	0	1	IN	0.2016	0.0476
GALLBLADDER	ORG013	B-Papilloma	770	2%	2	0	0	1	0	IN	0.7968	0.7643
HARDERIAN GL (2)	ORG014	B-Adenoma	130	12%	5	7	8	9	8	IN	0.2221	0.2087
KIDNEY (2)	ORG017	B-Tubular adenoma	775	1%	1	0	0	0	0	IN	1.0000	0.8484
LIVER	ORG026	M-Hepatocellular carcinom	466	9%	4	5	1	2	5	MX	0.3932	0.3770
LIVER	ORG026	B-Hepatocellular adenoma	53	20%	14	6	11	7	7	MX	0.8267	0.8160
LUNG/BRONCHUS	ORG027	M-Bronchoalveolar carcino	494	7%	3	4	1	4	3	MX	0.4892	0.4738
LUNG/BRONCHUS	ORG027	B-Bronchoalveolar adenoma	87	34%	13	21	16	13	21	IN	0.2003	0.1898
PANCREAS	ORG033	B-Islet cell adenoma	807	1%	1	0	0	0	1	IN	0.4001	0.3080
PITUITARY	ORG035	B-Adenoma, pars intermedi	847	1%	0	1	0	0	0	IN	1.0000	0.8147
PROSTATE	ORG036	B-Hemangioma	856	2%	2	0	0	0	0	IN	1.0000	0.9132
SPLEEN	ORG044	B-Hemangioma	727	.0%	0	0	0	0	1	IN	0.2031	0.0484
STOMACH	ORG045	M-Squamous cell carcinoma	782	.0%	0	0	0	0	1	IN	0.2016	0.0476
SUBCUTIS	ORG046	M-Sarcoma, NOS	187	1%	1	0	0	0	2	MX	0.1064	0.0581
SUBCUTIS	ORG046	M-Malignant schwannoma	364	1%	1	0	0	0	0	FA	1.0000	0.8357
SUBCUTIS	ORG046	M-Liposarcoma	495	1%	0	1	0	0	0	FA	1.0000	0.8405
SYSTEMIC	ORG047	M-Lymphoma	106	5%	4	1	2	7	4	MX	0.1883	0.1714
SYSTEMIC	ORG047	M-Histiocytic sarcoma	231	.0%	0	0	1	0	1	MX	0.1916	0.1477
SYSTEMIC	ORG047	M-Hemangiosarcoma	397	12%	6	6	4	4	2	MX	0.9513	0.9399
SYSTEMIC	ORG047	M-Mesothelioma	752	.0%	0	0	0	0	1	IN	0.2016	0.0476
TESTIS (2)	ORG048	B-Interstitial cell adeno	639	2%	2	0	2	4	1	IN	0.3741	0.3512
TESTIS (2)	ORG048	B-Hemangioma	750	.0%	0	0	1	0	0	IN	0.6250	0.6391
THYROID	ORG050	B-Follicular cell adenoma	374	1%	0	1	0	0	0	IN	1.0000	0.8484
THYROID	ORG050	M-Follicular cell carcino	380	.0%	0	0	0	0	1	IN	0.1842	0.0413

Number of Animals
Species: Mouse
Sex: Female

	Treatment Group					
	CTRL1	CTRL2	LOW	MED	HIGH	Total
	N	N	N	N	N	N
Week						
0-52	4	2	3	2	3	14
53-78	8	4	9	7	7	35
79-91	12	11	7	12	7	49
92-103	5	12	9	7	8	41
104-104	21	21	22	22	25	111
Total	50	50	50	50	50	250

Source: C:\CARC2\XAnimalX.txt

Analysis of Mortality
Species: Mouse
Sex: Female

	Dose														
	CTRL1			CTRL2			LOW			MED			HIGH		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
Week															
0-52	4	50	8.0	2	50	4.0	3	50	6.0	2	50	4.0	3	50	6.0
53-78	8	46	24.0	4	48	12.0	9	47	24.0	7	48	18.0	7	47	20.0
79-91	12	38	48.0	11	44	34.0	7	38	38.0	12	41	42.0	7	40	34.0
92-103	5	26	58.0	12	33	58.0	9	31	56.0	7	29	56.0	8	33	50.0
104-104	21	50	42.0	21	50	42.0	22	50	44.0	22	50	44.0	25	50	50.0

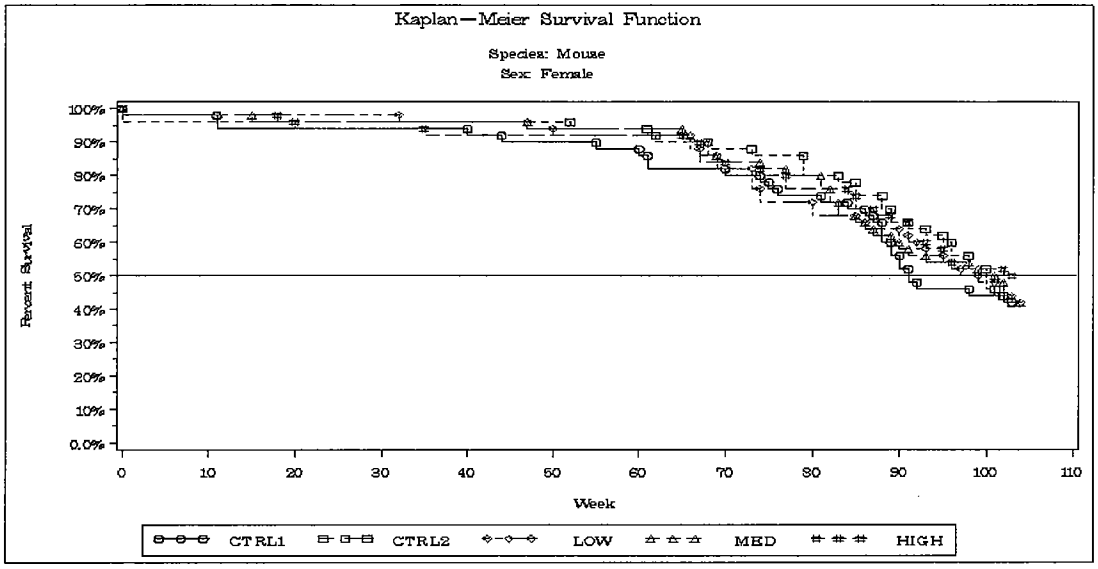
Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Mouse
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.57	0.4522
	Depart from Trend	0.29	0.9614
	Homogeneity	0.86	0.9306
Kruskal-Wallis	Dose-Mortality Trend	0.34	0.5572
	Depart from Trend	0.78	0.8542
	Homogeneity	1.12	0.8904

Source: C:\CARC2\XAnimalX.txt


Kaplan—Meier Survival Function
Species: Mouse
Sex: Female
Percent Survival
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0.0%
0
10
20
30
40
50
60
70
80
90
100
110
Week
CTRL1
CTRL2
LOW
MED
HIGH

Test for Dose-Tumor Positive Linear Trend

Source: Female Mouse Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL 1	CTRL 2	LOW	MED	HIGH	Tumor type	pValue (Exact)	pValue (Asymp)
ADRENAL (2)	ORG001	B-Spindle cell adenoma	759	2%	0	2	0	2	0	IN	0.7834	0.7541
BONE	ORG003	M-Osteosarcoma	881	.0%	0	0	2	0	0	FA	0.6923	0.6771
BRAIN	ORG006	M-Meningeal sarcoma	459	1%	0	1	0	0	0	FA	1.0000	0.8427
CECUM	ORG007	M-Leiomyosarcoma	825	.0%	0	0	1	0	0	IN	0.6216	0.6509
DUODENUM	ORG009	B-Adenoma	787	1%	1	0	2	0	0	IN	0.8440	0.8204
HARDERIAN GL (2)	ORG014	B-Adenoma	130	2%	1	1	1	5	2	IN	0.1631	0.1409
KIDNEY (2)	ORG017	B-Tubular adenoma	775	1%	0	1	0	0	0	IN	1.0000	0.8331
L.NODE-MESEN	ORG020	B-Hemangioma	842	1%	0	1	0	0	0	IN	1.0000	0.8580
LIVER	ORG026	M-Hepatocellular carcinom	466	.0%	0	0	0	0	1	IN	0.2252	0.0587
LIVER	ORG026	B-Hemangioma	497	1%	0	1	0	0	0	IN	1.0000	0.8506
LIVER	ORG026	B-Hepatocellular adenoma	53	3%	2	1	1	1	3	IN	0.2148	0.1894
LUNG/BRONCHUS	ORG027	M-Bronchoalveolar carcino	494	4%	1	3	0	3	0	MX	0.8647	0.8425
LUNG/BRONCHUS	ORG027	B-Bronchoalveolar adenoma	87	21%	9	12	12	10	9	MX	0.7549	0.7438
MAMMARY GLAND	ORG028	M-Carcinoma	522	1%	1	0	0	1	1	MX	0.3322	0.2845
MAMMARY GLAND	ORG028	B-Adenoma	566	.0%	0	0	1	1	0	IN	0.4604	0.4612
MAMMARY GLAND	ORG028	M-Malignant adenoacanthom	835	1%	1	0	0	0	0	IN	1.0000	0.8510
MAMMARY GLAND	ORG028	B-Adenoacanthoma	845	.0%	0	0	1	0	0	IN	0.6226	0.6518
MESENTERY	ORG031	B-Lipoma	826	.0%	0	0	1	0	0	IN	0.6216	0.6509
OVARY (2)	ORG032	M-Malignant granulosa cel	377	.0%	0	0	1	0	0	FA	0.6123	0.6353
OVARY (2)	ORG032	B-Cystadenoma	562	4%	1	3	1	1	0	IN	0.9555	0.9329
OVARY (2)	ORG032	B-Tubulostromal adenoma	611	6%	4	2	2	0	0	IN	0.9975	0.9885
OVARY (2)	ORG032	B-Luteoma	793	2%	0	2	1	1	0	IN	0.8587	0.8402
OVARY (2)	ORG032	B-Granulosa cell tumor	853	1%	1	0	0	0	0	IN	1.0000	0.8490
PANCREAS	ORG033	B-Islet cell adenoma	807	1%	1	0	0	1	0	IN	0.6724	0.6463
PITUITARY	ORG035	B-Adenoma	713	2%	1	1	2	2	1	IN	0.5853	0.5614
PITUITARY	ORG035	B-Adenoma,	847	.0%	0	0	0	0	1	IN	0.2294	0.0609

		pars intermedi										
STOMACH	ORG045	M-Carcinoma	297	1%	0	1	0	0	0	FA	1.0000	0.8409
STOMACH	ORG045	M-Squamous cell carcinoma	782	1%	0	1	0	0	0	IN	1.0000	0.8331
STOMACH	ORG045	B-Squamous papilloma	812	1%	0	1	2	0	2	IN	0.2459	0.2080
STOMACH	ORG045	B-Polypoid adenoma	860	1%	1	0	0	0	0	IN	1.0000	0.8331
SUBCUTIS	ORG046	M-Sarcoma, NOS	187	1%	0	1	0	0	0	FA	1.0000	0.8403
SUBCUTIS	ORG046	M-Malignant schwannoma	364	2%	0	2	0	0	0	FA	1.0000	0.9180
SYSTEMIC	ORG047	M-Lymphoma	106	22%	16	6	16	16	17	MX	0.1335	0.1256
SYSTEMIC	ORG047	M-Histiocytic sarcoma	231	9%	3	6	5	4	4	MX	0.6321	0.6200
SYSTEMIC	ORG047	M-Hemangiosarcoma	397	9%	3	6	4	5	5	MX	0.4909	0.4772
SYSTEMIC	ORG047	M-Leukemia, granulocytic	820	.0%	0	0	0	1	0	IN	0.4234	0.3961
THYROID	ORG050	B-Follicular cell adenoma	374	1%	0	1	0	0	0	IN	1.0000	0.8331
UTERUS	ORG054	M-Endometrial stromal sar	400	2%	1	1	2	3	1	MX	0.4723	0.4508
UTERUS	ORG054	M-Carcinoma	498	4%	2	2	0	1	1	MX	0.7687	0.7459
UTERUS	ORG054	B-Leiomyoma	505	3%	0	3	2	0	1	IN	0.7652	0.7414
UTERUS	ORG054	B-Endometrial stromal pol	549	12%	6	6	4	5	3	MX	0.8947	0.8823
UTERUS	ORG054	B-Hemangioma	559	1%	0	1	1	1	1	MX	0.3511	0.3287
UTERUS	ORG054	M-Leiomyosarcoma	570	3%	1	2	1	2	2	MX	0.3573	0.3339
UTERUS	ORG054	M-Malignant schwannoma	605	3%	3	0	1	0	1	IN	0.7583	0.7362
UTERUS	ORG054	M-Carcinoma, cervix	618	1%	1	0	1	1	0	IN	0.7337	0.7264
UTERUS	ORG054	M-Osteosarcoma	619	.0%	0	0	1	0	0	IN	0.5306	0.5860
UTERUS	ORG054	B-Fibroma	863	1%	0	1	0	0	1	IN	0.3844	0.2817
VAGINA	ORG055	B-Leiomyoma	816	.0%	0	0	0	0	1	IN	0.2252	0.0587

Number of Animals
Species: Rat
Sex: Male

	Treatment Group					
	CTRL1	CTRL2	LOW	MED	HIGH	Total
	N	N	N	N	N	N
Week						
0-52	4	5	4	4	11	28
53-78	18	15	15	17	16	81
79-91	17	12	16	10	14	69
92-100	11	11	10	12	11	55
101-101	15	22	20	22	13	92
Total	65	65	65	65	65	325

Source: C:\CARC2\XAnimalX.txt

Analysis of Mortality
Species: Rat
Sex: Male

	Dose														
	CTRL1			CTRL2			LOW			MED			HIGH		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
Week															
0-52	4	65	6.2	5	65	7.7	4	65	6.2	4	65	6.2	11	65	16.9
53-78	18	61	33.8	15	60	30.8	15	61	29.2	17	61	32.3	16	54	41.5
79-91	17	43	60.0	12	45	49.2	16	46	53.8	10	44	47.7	14	38	63.1
92-100	11	26	76.9	11	33	66.2	10	30	69.2	12	34	66.2	11	24	80.0
101-101	15	65	23.1	22	65	33.8	20	65	30.8	22	65	33.8	13	65	20.0

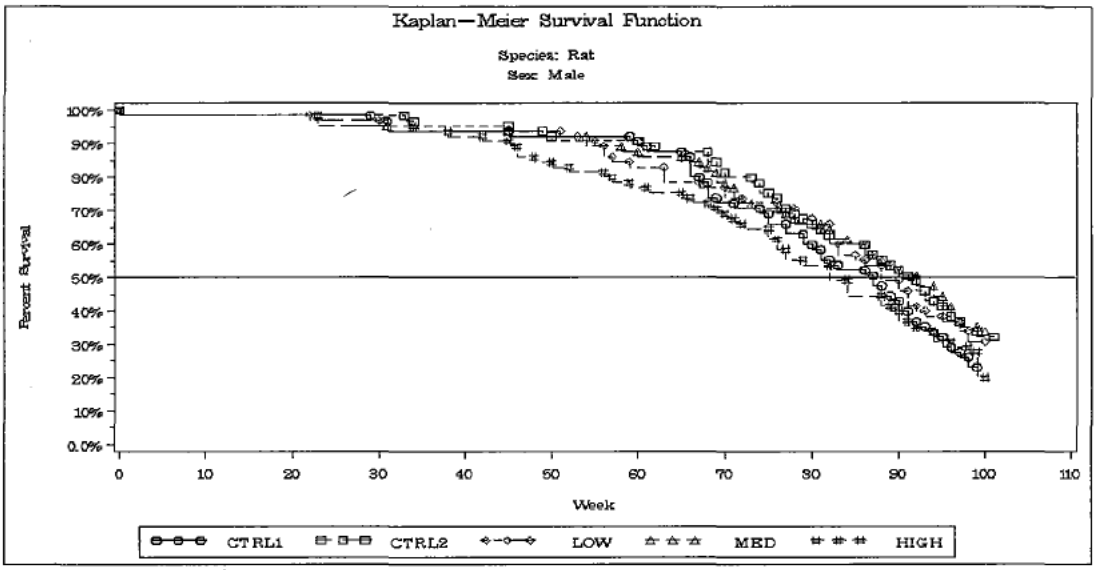
Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Rat
Sex: Male

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.34	0.2468
	Depart from Trend	4.23	0.2379
	Homogeneity	5.57	0.2337
Kruskal-Wallis	Dose-Mortality Trend	1.78	0.1825
	Depart from Trend	3.59	0.3095
	Homogeneity	5.37	0.2518

Source: C:\CARC2\XAnimalX.txt


Kaplan—Meier Survival Function
Species: Rat
Sex: Male
Percent Survival
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0.0%
0
10
20
30
40
50
60
70
80
90
100
110
Week
CTRL1
CTRL2
LOW
MED
HIGH

Test for Dose-Tumor Positive Linear Trend

Source: Male Rat Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL 1	CTRL 2	LOW	MED	HIGH	Tumor type	pValue (Exact)	pValue (Asymp)
ADRENAL (2)	ORG001	B-Pheochromocytoma	331	6%	4	4	6	2	1	IN	0.9500	0.9363
ADRENAL (2)	ORG001	B-Cortical adenoma	571	8%	0	1	0	1	0	IN	0.6963	0.6723
ANUS	ORG002	B-Schwannoma	466	0%	0	0	1	0	0	IN	0.5797	0.6129
ANUS	ORG002	M-Leiomyosarcoma	528	0%	0	0	1	0	0	FA	0.5892	0.6157
BONE-FEMUR	ORG004	M-Osteosarcoma	685	8%	0	1	0	0	0	IN	1.0000	0.8455
BRAIN	ORG006	M-Schwannoma, malignant	459	0%	0	0	1	0	0	FA	0.5972	0.6148
BRAIN	ORG006	B-Astrocytoma	549	0%	0	0	1	1	1	MX	0.1450	0.1160
BRAIN	ORG006	B-Granular cell tumor	560	8%	1	0	0	0	2	MX	0.1039	0.0586
BRAIN	ORG006	M-Anaplastic glioma	686	8%	0	1	1	0	0	MX	0.8409	0.8027
BRAIN	ORG006	M-Ganglioneuroma	97	0%	0	0	1	0	0	FA	0.5968	0.6291
CAVITY-ABDOM	ORG007	M-Sarcoma, NOS	534	8%	0	1	0	0	0	FA	1.0000	0.8392
CAVITY-ABDOM	ORG007	M-Schwannoma, malignant	776	0%	0	0	0	0	1	FA	0.1823	0.0411
CECUM	ORG008	M-Osteosarcoma	543	0%	0	0	0	1	0	IN	0.3478	0.3537
EAR	ORG011	M-Carcinoma, Zymbal's gla	122	8%	1	0	0	0	0	IN	1.0000	0.8873
HEAD	ORG014	X-Schwannoma, malignant	739	8%	1	0	0	0	0	IN	1.0000	0.8418
HEART	ORG015	B-Intramural schwannoma	731	0%	0	0	0	0	1	IN	0.1429	0.0268
KIDNEY (2)	ORG018	B-Tubular adenoma	568	8%	0	1	1	0	0	IN	0.8269	0.7977
KIDNEY (2)	ORG018	M-Liposarcoma	672	8%	0	1	1	0	0	MX	0.8512	0.8136
KIDNEY (2)	ORG018	B-Lipoma	674	0%	0	0	0	2	0	IN	0.3652	0.2730
LIVER	ORG024	M-Hepatocellular carcinom	451	2%	2	1	2	1	0	MX	0.9030	0.8767
LIVER	ORG024	M-Cholangiocarcinoma	497	8%	1	0	1	0	0	MX	0.8354	0.8114
LIVER	ORG024	B-Hepatocellular adenoma	630	2%	2	1	0	0	1	IN	0.7097	0.6809
LUNG/BRONCHUS	ORG025	M-Squamous cell carcinoma	148	0%	0	0	0	0	1	FA	0.1867	0.0419
LUNG/BRONCHUS	ORG025	X-Giant cell tumor	417	0%	0	0	0	0	1	IN	0.1975	0.0471
LUNG/BRONCHUS	ORG025	B-Bronchoalveolar adenoma	474	0%	0	0	0	0	2	IN	0.0370	0.0079
LUNG/BRONCHUS	ORG025	B-Pleural mesothelioma	721	8%	1	0	0	0	0	IN	1.0000	0.8410
LUNG/BRONCHUS	ORG025	M-Sarcoma, NOS	775	0%	0	0	0	1	0	FA	0.3868	0.3501
MAMMARY GLAND	ORG026	B-Fibroadenoma	349	0%	0	0	1	2	0	IN	0.3657	0.3316
MAMMARY GLAND	ORG026	M-Carcinoma	382	8%	0	1	0	0	0	IN	1.0000	0.8395
PANCREAS	ORG030	B-Islet cell adenoma	327	8%	7	3	3	7	6	IN	0.2032	0.1883

PANCREAS	ORG030	M-Islet cell carcinoma	452	5%	3	3	0	1	2	IN	0.7144	0.6962
PANCREAS	ORG030	M-Acinar carcinoma	663	.8%	0	1	0	0	0	IN	1.0000	0.8486
PITUITARY	ORG032	B-Adenoma	1	52%	29	38	36	34	34	MX	0.4811	0.4741
PITUITARY	ORG032	M-Schwannoma, malignant	178	.0%	0	0	1	0	0	FA	0.6014	0.6246
PITUITARY	ORG032	M-Carcinoma	253	.8%	1	0	2	0	0	MX	0.8342	0.7992
PROSTATE	ORG033	M-Accessory sex gland car	444	.8%	1	0	0	0	0	FA	1.0000	0.8377
RIB	ORG036	M-Osteosarcoma	736	.0%	0	0	0	1	0	IN	0.3804	0.3190
SKIN-MISC	ORG042	M-Malignant fibrous histi	224	.0%	0	0	0	0	1	IN	0.3929	0.1363
SKIN-MISC	ORG042	B-Sebaceous cell adenoma	307	.0%	0	0	1	1	0	IN	0.4510	0.4519
SKIN-MISC	ORG042	M-Basal cell carcinoma	368	.8%	0	1	0	0	0	IN	1.0000	0.8418
SKIN-MISC	ORG042	M-Squamous cell carcinoma	418	.0%	0	0	1	0	0	IN	0.5797	0.6129
SKIN-MISC	ORG042	B-Keratoacanthoma	458	3%	0	4	1	1	1	IN	0.7502	0.7284
SKIN-MISC	ORG042	B-Squamous papilloma	726	.8%	1	0	0	0	1	IN	0.3192	0.2353
STOMACH	ORG045	X-Adenocarcinoma	563	.0%	0	0	1	0	0	IN	0.5797	0.6129
STOMACH	ORG045	M-Carcinoma	619	.8%	1	0	0	0	0	IN	1.0000	0.8446
STOMACH	ORG045	M-Malignant neuroendocrin	735	.0%	0	0	1	0	0	IN	0.5978	0.6048
SUBCUTIS	ORG046	M-Sarcoma, NOS	283	.8%	0	1	0	1	1	IN	0.2765	0.2272
SUBCUTIS	ORG046	B-Fibroma	308	2%	0	2	3	3	1	IN	0.4297	0.4092
SUBCUTIS	ORG046	B-Schwannoma	659	.0%	0	0	1	0	0	IN	0.5797	0.6129
SUBCUTIS	ORG046	B-Lipoma	669	2%	2	1	1	1	0	IN	0.9061	0.8776
SUBCUTIS	ORG046	M-Malignant schwannoma	684	.0%	0	0	1	0	0	IN	0.5797	0.6129
SUBCUTIS	ORG046	M-Fibrosarcoma	748	.0%	0	0	0	1	0	IN	0.3804	0.3190
SYSTEMIC	ORG047	M-Lymphoma	138	3%	1	3	0	1	1	FA	0.7513	0.7284
SYSTEMIC	ORG047	M-Histiocytic sarcoma	189	2%	1	1	1	3	3	MX	0.0757	0.0575
SYSTEMIC	ORG047	M-Hemangiosarcoma	572	.0%	0	0	1	1	0	IN	0.4243	0.4215
SYSTEMIC	ORG047	M-Mesothelioma	637	.0%	0	0	0	2	0	MX	0.3424	0.2557
TAIL	ORG048	B-Squamous papilloma	742	.8%	1	0	0	0	0	IN	1.0000	0.8418
TESTIS (2)	ORG049	B-Interstitial cell adeno	566	4%	2	3	1	1	1	IN	0.8450	0.8236
THYROID	ORG051	B-C-cell adenoma	256	4%	1	4	7	6	7	IN	0.0257	0.0195
THYROID	ORG051	B-Follicular cell adenoma	465	2%	2	0	4	2	0	IN	0.7667	0.7464
THYROID	ORG051	M-Follicular cell carcino	562	.0%	0	0	1	2	1	IN	0.1368	0.1056
THYROID	ORG051	B-Ganglioneuroma	646	.0%	0	0	1	0	0	IN	0.6000	0.6353
THYROID	ORG051	M-C-cell carcinoma	730	2%	1	1	0	2	0	IN	0.6943	0.6657
URINARY BLADDER	ORG053	B-Transitional cell papil	728	.0%	0	0	0	1	0	IN	0.3846	0.3228
VERTEBRAE	ORG056	M-Chondrosarcoma	536	.0%	0	0	0	1	0	FA	0.4010	0.3578

Number of Animals
Species: Rat
Sex: Female

	Treatment Group					
	CTRL1	CTRL2	LOW	MED	HIGH	Total
	N	N	N	N	N	N
Week						
0-52	2	1	2	3	7	15
53-78	15	13	19	16	15	78
79-91	17	20	17	12	13	79
92-103	16	11	9	17	15	68
104-104	15	20	18	17	15	85
Total	65	65	65	65	65	325

Source: C:\CARC2\XAnimalX.txt

Analysis of Mortality
Species: Rat
Sex: Female

	Dose														
	CTRL1			CTRL2			LOW			MED			HIGH		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
Week															
0-52	2	65	3.1	1	65	1.5	2	65	3.1	3	65	4.6	7	65	10.8
53-78	15	63	26.2	13	64	21.5	19	63	32.3	16	62	29.2	15	58	33.8
79-91	17	48	52.3	20	51	52.3	17	44	58.5	12	46	47.7	13	43	53.8
92-103	16	31	76.9	11	31	69.2	9	27	72.3	17	34	73.8	15	30	76.9
104-104	15	65	23.1	20	65	30.8	18	65	27.7	17	65	26.2	15	65	23.1

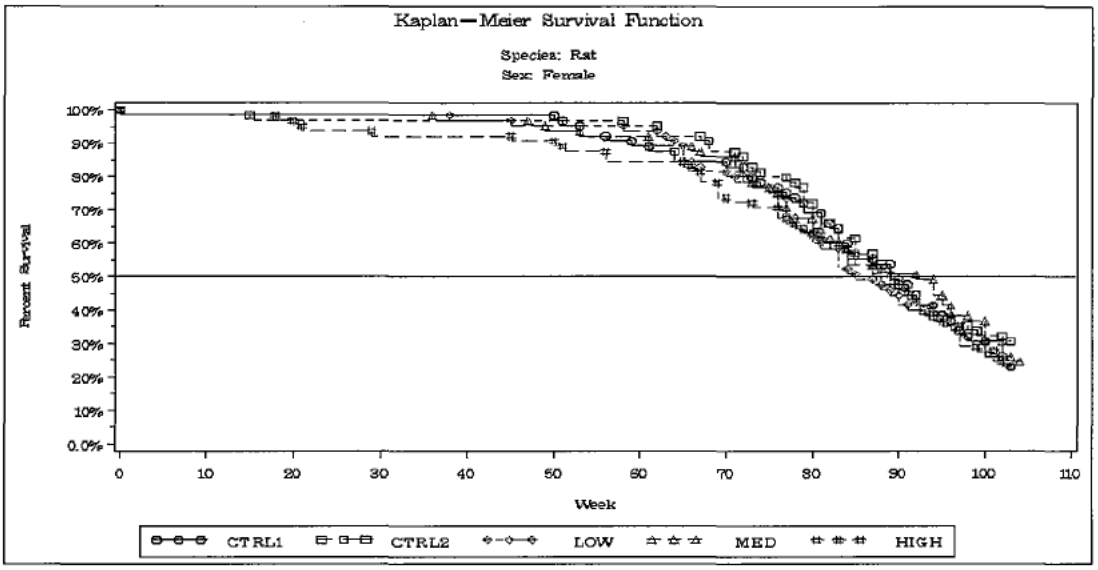
Dose-Mortality Trend Tests

This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute

Species: Rat
Sex: Female

Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.46	0.4966
	Depart from Trend	0.65	0.8852
	Homogeneity	1.11	0.8925
Kruskal-Wallis	Dose-Mortality Trend	0.75	0.3856
	Depart from Trend	0.86	0.8360
	Homogeneity	1.61	0.8072

Source: C:\CARC2\XAnimalX.txt


Kaplan—Meier Survival Function
Species: Rat
Sex: Female
Percent Survival
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0.0%
0
10
20
30
40
50
60
70
80
90
100
110
Week
CTRL1
CTRL2
LOW
MED
HIGH

Test for Dose-Tumor Positive Linear Trend

Source: Female Rat Data

Organ Name	Organ Code	Tumor Name	Tumor Code	Natural Rate (in ctrl group)	CTRL 1	CTRL 2	LOW	MED	HIGH	Tumor type	pValue (Exact)	pValue (Asymp)
ADRENAL (2)	ORG001	B-Pheochromocytoma	331	0%	0	0	0	1	0	IN	0.3765	0.3439
ADRENAL (2)	ORG001	B-Cortical adenoma	571	8%	0	1	2	3	1	IN	0.2695	0.2416
ADRENAL (2)	ORG001	M-Cortical carcinoma	718	2%	1	1	0	0	0	MX	1.0000	0.9129
BONE-FEMUR	ORG004	M-Osteosarcoma	685	8%	1	0	0	0	0	IN	1.0000	0.8598
BRAIN	ORG006	B-Astrocytoma	549	0%	0	0	1	0	0	IN	0.5316	0.5764
BRAIN	ORG006	B-Granular cell tumor	560	8%	1	0	0	1	0	IN	0.6569	0.6410
BRAIN	ORG006	M-Anaplastic glioma	686	8%	0	1	0	0	0	IN	1.0000	0.8530
EAR	ORG011	M-Carcinoma, Zymbal's gla	122	2%	2	0	1	0	0	IN	0.9569	0.9123
HEART	ORG015	M-Atriocaval mesothelioma	708	0%	0	0	0	1	0	FA	0.4118	0.3533
JEJUNUM	ORG017	B-Leiomyoma	698	8%	0	1	0	0	0	IN	1.0000	0.8530
KIDNEY (2)	ORG018	M-Tubular carcinoma	706	2%	1	1	0	0	0	IN	1.0000	0.8981
L.NODE-MESEN	ORG021	B-Hemangioma	705	8%	0	1	1	0	0	IN	0.8390	0.8200
LIVER	ORG024	M-Hepatocellular carcinom	451	0%	0	0	1	0	0	IN	0.5882	0.6134
LIVER	ORG024	B-Hepatocellular adenoma	630	0%	0	0	1	3	0	IN	0.3625	0.3387
LUNG/BRONCHUS	ORG025	B-Bronchoalveolar adenoma	474	0%	0	0	0	1	0	IN	0.3165	0.3077
LUNG/BRONCHUS	ORG025	M-Osteosarcoma	681	8%	1	0	0	0	0	IN	1.0000	0.8530
MAMMARY GLAND	ORG026	B-Fibroadenoma	349	50%	36	29	34	32	22	IN	0.9669	0.9645
MAMMARY GLAND	ORG026	M-Carcinoma	382	18%	10	13	17	17	15	IN	0.1504	0.1416
MAMMARY GLAND	ORG026	B-Adenoma	394	3%	2	2	2	4	4	IN	0.2154	0.1951
MAMMARY GLAND	ORG026	B-Intraductal papilloma	707	8%	0	1	0	0	2	IN	0.1208	0.0710
MAMMARY GLAND	ORG026	B-Fibroma	754	0%	0	0	2	0	0	IN	0.6569	0.6410
OVARY (2)	ORG029	B-Sertoliform tubular ade	475	0%	0	0	1	0	1	IN	0.1765	0.1331
OVARY (2)	ORG029	B-Thecoma	601	2%	2	0	0	1	0	IN	0.8034	0.7784
OVARY (2)	ORG029	B-Mesovarial leiomyoma	769	8%	0	1	0	0	0	IN	1.0000	0.8361
OVARY (2)	ORG029	B-Granulosa cell tumor	779	0%	0	0	0	1	0	IN	0.3765	0.3439
PANCREAS	ORG030	B-Islet cell adenoma	327	5%	4	2	2	1	2	IN	0.8118	0.7931
PANCREAS	ORG030	M-Islet cell carcinoma	452	8%	1	0	0	0	0	IN	1.0000	0.8127

PITUITARY	ORG032	B-Adenoma	1	75%	47	50	42	49	48	MX	0.1857	0.1803
PITUITARY	ORG032	M-Carcinoma	253	5%	5	1	8	8	4	MX	0.2376	0.2240
PITUITARY	ORG032	M-Meningeal sarcoma	683	.0%	0	0	1	0	0	FA	0.5981	0.6201
SKIN-MISC	ORG042	B-Fibroma	133	.0%	0	0	0	1	0	IN	0.3165	0.3077
SKIN-MISC	ORG042	M-Malignant fibrous histi	224	.0%	0	0	0	1	0	IN	0.3765	0.3439
SKIN-MISC	ORG042	M-Squamous cell carcinoma	418	.0%	0	0	0	2	0	IN	0.6343	0.5026
SKIN-MISC	ORG042	B-Keratoacantho ma	458	.0%	0	0	0	0	1	IN	0.1765	0.0373
SKIN-MISC	ORG042	M-Adnexal carcinoma	473	.0%	0	0	0	0	1	IN	0.1923	0.0443
SPLEEN	ORG044	B-Hemangioma	703	.8%	1	0	0	0	0	IN	1.0000	0.8530
STOMACH	ORG045	B-Adenoma	717	.0%	0	0	0	0	1	IN	0.2206	0.0605
SUBCUTIS	ORG046	M-Sarcoma, NOS	283	2%	1	1	1	1	1	IN	0.5470	0.5246
SUBCUTIS	ORG046	B-Fibroma	308	.8%	1	0	0	3	0	IN	0.5064	0.4684
SUBCUTIS	ORG046	M-Fibrous histiocytoma	584	.8%	0	1	1	0	0	IN	0.8071	0.7826
SUBCUTIS	ORG046	B-Lipoma	669	.8%	1	0	0	0	0	IN	1.0000	0.8530
SUBCUTIS	ORG046	M-Malignant schwannoma	684	.8%	0	1	0	0	0	IN	1.0000	0.8361
SYSTEMIC	ORG047	M-Lymphoma	138	2%	2	0	1	0	1	MX	0.6379	0.6155
SYSTEMIC	ORG047	M-Histiocytic sarcoma	189	2%	0	2	0	0	2	MX	0.2348	0.1918
SYSTEMIC	ORG047	M-Hemangiosarco ma	572	.0%	0	0	1	0	0	FA	0.5889	0.6196
THYMUS	ORG050	B-Thymoma	374	.0%	0	0	1	0	0	FA	0.5856	0.6177
THYROID	ORG051	B-C-cell adenoma	256	15%	8	11	8	8	10	IN	0.3450	0.3327
THYROID	ORG051	B-Follicular cell adenoma	465	.8%	1	0	1	1	0	IN	0.6687	0.6645
THYROID	ORG051	B-Ganglioneurom a	646	.8%	1	0	0	1	1	IN	0.2987	0.2465
THYROID	ORG051	M-C-cell carcinoma	730	.8%	1	0	1	0	0	IN	0.8333	0.8029
UTERUS	ORG054	B-Leiomyoma	422	.0%	0	0	1	0	0	IN	0.6316	0.6342
UTERUS	ORG054	B-Endometrial stromal pol	428	7%	3	6	1	3	2	IN	0.8347	0.8185
UTERUS	ORG054	M-Malignant schwannoma	695	.8%	1	0	0	0	1	MX	0.4134	0.3097
UTERUS	ORG054	B-Fibroma	771	.0%	0	0	0	1	0	IN	0.3765	0.3439
UTERUS	ORG054	M-Sarcoma, NOS	772	.0%	0	0	0	0	1	IN	0.1765	0.0373
VAGINA	ORG055	B-Fibroma	763	.0%	0	0	0	0	1	IN	0.1923	0.0443
VERTEBRAE	ORG056	M-Chordoma	697	.0%	0	0	0	0	1	IN	0.2206	0.0605

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/s/

Kun He
4/17/01 09:46:50 AM
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4/17/01 10:23:22 AM
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George Chi
4/17/01 01:48:06 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-599/S002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

MF 8/10/00

CLINICAL PHARMACOLOGY &BIOPHARMACEUTICS REVIEW
PHARMACOMETRICS REVIEW

NDA 20-599	**Submission Dates:** October 8, 1996, December 23, 1996, November 4, 1998, December 2, 1998, May 9, 2000.
Drug Name:	Rilutek (riluzole)
Formulation:	Tablet 50 mg
Dosage:	50 mg BID
Applicant:	Rhone-Poulenc Rorer
Consult:	Results of the study RP 54274-301 "Population Pharmacokinetics Analysis of Riluzole"
Pharmacometrics Specialist:	Elena V. Mishina, Ph.D.

Preamble/Background:

Riulutek was approved 12/12/1995 for the treatment of amyotropic lateral sclerosis (ALS). In order to fulfil Phase IV commitments for the label update, the sponsor submitted for review new data from the study RP 54274-301 "Population Pharmacokinetics Analysis of Riluzole". Population data analysis was performed by the sponsor for the assessment of the effects of age, gender, cigarette smoking, and use of other drugs on pharmacokinetics (PK) of riluzole.

Objectives:

- to define a basic population PK model, estimate PK parameters and assess inter- and intra-patient variabilities;
- to generate individual estimates of clearance and drug exposure;
- to investigate statistically if clearance depends on time and dose;
- to investigate the effect of patho-physiologic covariates on riluzole PK parameters.

Methods:

This was a double blind, placebo-controlled, parallel group dose ranging Phase 3 study. Three dose levels were evaluated in four parallel groups of patients receiving

25 mg BID (50 mg/day);
50 mg BID (100 mg/day);
100 mg BID (200 mg/day);
placebo BID.

All patients were diagnosed with ALS. Patients with AST and/or ALT >2 upper limit and creatinine higher than 200 mcmol/L were excluded from the study. Concurrent treatment with any enzyme inducers or inhibitors was contraindicated.

Originally the sponsor intended to accrue at least 300 patients (225 receiving riluzole) in several centers in US, Canada, Germany and UK. The final submitted report contained the population pharmacokinetic analysis of the riluzole plasma data of 128 patients obtained from the eight North American centers.

The following covariates were recorded and included in the data analysis:

Demographics (age, gender, race, weight);
Laboratory measurements:
liver function tests: SGOT (ALT), SGPT (AST), γ GT, alkaline phosphatase, total and direct bilirubin (baseline and then every 2 months);
creatinine, total proteins and albumin (baseline and then every 2 months);
Concomitant medications
Disease form at onset (bulbar vs limb)
Occurrence of gastrostomy.

Blood Sampling and Assay:

Sparse sampling with the collection of 4 plasma samples per patient at 2 visit days (2 per visit with the interval of 1 to 4 hours between samples). These intervals were allowed to vary between patients. For some patients the blood samples were taken in the morning and for the other patients in the afternoon. Riluzole was assayed in plasma samples by HPLC with UV detection, where the limit of quantitation was 5 ng/mL, CV < 8.2%.

Data Analysis:

The applicant firstly created a structural model. Nonlinear mixed effect model software (NONMEM version IV, level 2.0) was used running on a Digital DEC alpha station 2100 5/250 under the open VMS operating system. The applicant evaluated both one- and two-compartmental models with first order absorption and used parameterization with physiologic parameters (clearance and volume(s) of distribution). The applicant chose a proportional model for the inter-patient variability for clearance and volume of distribution, and the variance-covariance matrix was modeled either as diagonal or as a full matrix with BLOCK option (in the final model). The applicant modeled an inter-occasion variability for both clearance and volume of distribution assuming that the same variance estimate was used to several distributions jointly.

$$CL_{jk} = \tilde{CL}_{jk} \exp(\eta_{jCL} + \kappa_{jkCL})$$

where η_{jkCL} denotes the proportional difference between the true parameter (CL_{jk}) of individual j on occasion k and the typical value ($\hat{CL}_{jk}$) for an individual in the population with covariates equal to those of individual j at occasion k. The κ_{jkCL} are random variables with zero mean and variance π^2 and model between occasion differences within an individual. The π's also are the diagonal elements of the Ω matrix.

Proportional models for residual variability was evaluated:

$$Cp_{ij} = \tilde{C}\, p_{ij}(1+\varepsilon_{ij})$$

where Cp_{ij} and $\hat{C}p_{ij}$ are the i-th measured and modeled predicted concentrations for patient j and ε_{ij} denoted the residual intra-patient random error with zero mean and variance σ^2.

Alternative combined proportional and additive model for residual variability was evaluated:

$$Cp_{ij} = \tilde{C}\, p_{ij}(1+\varepsilon_{1ij}) + \varepsilon_{2ij}$$

The notations are the same as above but ε_{1ij} and ε_{2ij} denote the residual intra-patient random error for constant CCV part and the additive part with respective variances σ_1^2 and σ_2^2.

For the estimation methods both first order (FO) and first order conditional (FOCE) methods were used in the model. Individual patient parameters were obtained with a POSTHOC option. For the model diagnostics, the plots predicted vs observed plasma concentrations (PRED vs DV), weighted residuals (WRES) vs time and PRED, DV and PRED (as a smooth line) vs TIME were examined visually. For the individual estimations, the plots of individual predicted vs observed plasma concentrations, individual weighted residuals (IWRES) vs time and IPRED, DV and IPRED vs TIME with PRED as a smooth line were examined.

Then the applicant created a covariate model based on testing of the hypothesis of the likelihood ratio test to discriminate among the alternative models. The covariates were tested one by one, the significant covariates were incorporated into the model. After the finalizing of the full model, the significance of each of the covariates was tested by removing them from the model one by one. The alternative models were compared based on the log likelihood test. At the high level of sensitivity (p=0.005), 7.8 unit difference in the objective function was required for the test of statistical significance. At the screening stage, the level of sensitivity was assumed as p=0.05 (Δ in OFV 3.8).

Continuous covariates were modeled as for clearance

$$TrueParameter = \Theta_1 + \Theta_2 \cdot (Covariate - Median)$$

and dichotomic covariates were modeled as

$$TrueParameter = \Theta_1 \cdot (1 - \Theta_2 \cdot Covariate)$$

Time and dose dependence were tested as follows:

$$TrueParameter = [final\_model] + \Theta_x \cdot DURT$$

$$TrueParameter = [final\_model] \cdot (1 - \Theta_x \cdot D25) \cdot (1 - \Theta_y \cdot D50) \cdot (1 - \Theta_z \cdot D100)$$

where DURT is duration of treatment (in days) at the time of the visit and D25, D50 and D100 are the indicator variables equal to 1 if the corresponding dose was given, and 0 otherwise.

Although the riluzole plasma concentration data were obtained at the different time points throughout the day, the applicant did not attempt to consider the possible influence of the circadian variability in the parameters.

Influence of the covariates on clearance was examined by stepwise multiple regression (SAS version 6.08, Poc MIXED). Mixed effect linear modeling analysis is a generalization of standard linear models (as implemented in Proc GLM of SAS) that allow the assessment of several random effects instead of just one. In the proposed model, IIV was considered as a random effect, and visit month and dose level were considered as fixed effects. The distribution of individual clearance estimates was lognormal.

$$\log Cl_{jk} = \alpha_0 + \sum_{l=1}^{n} \alpha_l \cdot X_l + \eta_j + \kappa_{jk}$$

where α_0 is the intercept, α_1 is a regression coefficient for fixed effect X1 and η and κ denote inter-patient and inter-visit random effects as described in the NONMEM analysis. Restricted maximal likelihood was used for the estimation of α_0, α_1, var(η), and var(κ). A Fisher's statistics was used to test the significance of fixed effects (Applicant's Table 9, Appendix 1).

Results:

Database:
In the eight North American centers, 707 blood samples were obtained from the 142 patients receiving riluzole, and 245 samples were obtained from the patients receiving placebo. The final database contained 526 riluzole plasma measurements from 128 patients drawn at 347 different visits. Hundred patients were studied over 179 visits. The applicant reported that plasma samples were collected in about half of all patients (68) on 3 separate visits.

In the data file submitted for the review, only two patients (ID #17048, data on 2, 4, and 6 months, and ID #18027, data on 6, 8, and 10 months) have riluzole plasma concentrations data on the three occasions.

Basic population model:

In the data set, the data characterizing the absorption phase were very limited, and the applicant failed to obtain the realistic estimates of k_a. Assuming the high rate of riluzole absorption, the applicant fixed k_a value at $5h^{-1}$. Poor study design did not allow a proper assessment of k_a. Thus the arbitrary chosen fixed value for k_a probably impacted on the poor population fit obtained by the applicant in the final model.

The applicant has chosen a one-compartmental model over a two-compartmental model. This choice has been made based on "not very pronounced biphasic nature of the plot of riluzole concentration vs time" and difficulties, which the applicant claimed to have in obtaining the precise estimates.

AIC criteria calculated with

$$\Delta AIC = 2 \cdot (P_1 - P_2) + (OFV_1 - OFV_2)$$

for the comparison of run 4 vs run 1 (two- vs one compartmenal model, FO method) reported by the applicant in Tables 4 and 5 (Appendix):

$$\Delta AIC = 2 \cdot (8 - 5) + (-1479 + 1441) = -32$$

ΔAIC is negative. This means that the two-comparmentsl model should be chosen for the further development.

The applicant claimed that two-compartmental model had much higher variability on the parameters.

Variabilities on clearance and volume of distribution listed in the outputs of runs 1 and 4 (Tables 4 and 5, Appendix 1) were similar for both models except for the variability on intercompartmental blood flow (run 4).
Moreover, riluzole pharmacokinetics has been described with the two-compartmental model in the literature.
Reference:
A comparison of the pharmacokinetics and tolerability of riluzole after repeat dose administration in healthy elderly and young volunteers. Le Liboux A, Cachia JP, Kirkesseli S, Gautier JY, Guimart C, Montay G, Peeters PA, Groen E, Jonkman JH, Wemer J. J Clin Pharmacol. 1999 May;39(5):480-6.

At the first step, the applicant considered the data from each visit independently, and then introduced inter-occasion variability for each of the occasions (up to three). In the paper published based on this study, the authors recognized that two-compartmental model "substantially improved fit" but it could not run with FOCE estimation method.

Reference:
Population pharmacokinetics of riluzole in patients with amyotrophic lateral sclerosis. Bruno R, Vivier N, Montay G, Le Liboux A, Powe LK, Delumeau JC, Rhodes GR. Clin Pharmacol Ther. 1997 Nov; 62(5):518-26.

Another reason, which the applicant has not mentioned, was the limitation in the number of ETAs of 10 permitted by the program NONMEM version 4. For the model with inter-occasion variability, this number limits the model choice to one-compartmental. The applicant selected the one-compartmental model; however, this choice was not based on the appropriateness of the model but was dictated by the limitation of software.

For the evaluation of the goodness of fit, the applicant presented the plots of IPRED vs observed plasma concentration, IWRES vs IPRED and time.

The plots of individual predicted plasma concentration or individual weighted residuals are not the most informative for the assessment of goodness of fit for the population model. Moreover, these plots usually look better than the plots describing the whole population. The plots of the population predicted (PRED) vs observed plasma concentrations and WRES vs PRED and time should be used instead. These plots were made by the FDA and are shown in the Appendix 2, Figures 1-4. The plot of population predicted vs observed riluzole plasma concentrations (final model, FDA assessment, Appendix 2) shows the unequal distribution around the line of identity. The final model underestimated the riluzole plasma concentrations at high concentrations. Overestimation of the riluzole plasma concentrations at the early times most likely occurs due to the fixed k_a parameter.

IOV model:

The applicant modeled an inter-occasion variability for both clearance and volume of distribution assuming that the same variance estimate was used for several distributions jointly. The applicant did not explain the reason for this assumption and it is not obvious why the variance for clearance and volume of distribution should be the same at different occasions. The model with IOV had a significant drop in the objective function values (both with FO and FOCE methods, Table 6, Appendix 1). Additionally, the inter-subject varibilities as well as residual variability decreased with the use of IOV.
The applicant used the following model:

The FDA reviewer used a more general model for inter-occasion variability, where OMEGA BLOCK function was used to pair the variabilities on clearance and volume of distribution on each occasion (Appendix 2):

The best OFV reported by the applicant was –1779 (Table 11, Appendix 1). However, when the FDA re-ran the submitted control file using the applicant's data file and NONMEM version 5.0, the best OFV was –1767. When the IOV part of the applicant's

final model was changed according to the FDA model, the run converged with the OFV – 1797, which is 30 units smaller (significant difference) than the OFV obtained with the applicant's IOV model (OFV –1767). Please see Appendix 2.

Covariate Analysis

The applicant performed an appropriate analysis of the influence of different (demographics, disease, and liver, and kidney function associated) covariates on clearance.

Graphical representation of the influence of the covariate is assessed by the FDA, Figures 5-8, Appendix 2.

Gender was found to have the strongest influence on clearance. In the studied population, a typical female patient had on average 30% lower clearance in comparison with a typical male patient (Figure 6, Appendix 2). Another important covariate was smoking status.

The FDA model estimated the increase in clearance values for smokers in comparison with non-smokers to be 20% (the applicant's model calculated this increase to be 36%). Please see Appendix 2, Figure 7. In the studied population of 128 ALS patients, there were 19 smokers (8 females and 11 males), which is less than 15% of the total number of patients included in the analysis.

Riluzole clearance was also related to bilirubin and albumin levels in plasma (Figure 5, Appendix 2). The clearance values were lower in the patients with the decreased albumin plasma levels, which is related to the liver impairment. The influence of treatment duration, age, and transaminase plasma concentrations on clearance values was negligible.

The parameter estimates obtained by the FDA were similar with the applicant's findings. Although it was stated in the study objectives, the applicant did not evaluate the potential effect of in vitro inhibitors of riluzole metabolism (the available data were not sufficient to perform modeling).

Table 1. Comparison of parameter estimates, standard errors of parameter estimates, and coefficients of variations obtained by the firm and the FDA

Parameter	Clearance, L/h/m2		Volume of Distribution, L		Gender		Smoking	
	Firm	FDA	Firm	FDA	Firm	FDA	Firm	FDA
Estimate	51.5	51.4	371	362	0.317	0.294	0.363	0.200
CV, % (IIV)	42.2	42.2	64.9	61.7				
CV, % (IOV)	24.1	19.6 18.9 98.1	34.2	42.2 35.5 304				
Standard Error of Estimate	3.8	4.03	36.3	38.8	0.648	6.9	0.166	0.166
SE, %	7.4	7.8	10.0	10.45	20.4	23.4	45.7	83
Confidence Interval 95%	44.1 - 58.9	43.5 - 59.3	291 - 433	295 - 447	0.190 - 0.444	0.159 - 0.429	0.038 - 0.688	-0.125 - 0.525

Table 1 shows the comparison of parameter estimates, standard errors of parameter estimates, and coefficients of variations obtained by the applicant and the FDA (final model). Both models give similar results; however, the lower OFV (-1797 vs –1767) is in favor of the FDA IOV model. Inter-individual and inter-occasion variabilities were comparable for both models with the exclusion of high IOV for the occasion 3 (FDA model). This occurs probably due to that only two patients out of 128 had the drug plasma concentration measurements on three occasions. Additionally, 95% confidence intervals (CI) were calculated for parameters describing gender and smoking effect. For the applicant model, confidence intervals were more skewed than for the FDA model. The hypothesis that parameters for gender (Θ_9) and smoking (Θ_{10}) were significantly different from 0 is more firm for the FDA model (CI for gender is closer to the 0, and CI for smoking includes 0).

Exploratory data analysis:

The applicant performed the correlation analysis of clinical covariates and individual parameter estimates. Table 9 (Appendix 1) shows the results of the univariate linear regression analysis of CL vs patho-physiological covariates. This analysis confirmed the findings of NONMEM data analysis regarding the strong influence of gender, and significant effects of smoking factor, creatinine and bilirubin plasma levels, and also body weight.

Conclusions:

Overall, despite of the model miss-specification, the estimation of clearance values seems reasonable; however, volume of distribution values and plasma elimination half-life values were underestimated. Covariate analysis was appropriately performed, and the strong gender differences (30% lower clearance in female in comparison with male patients) were confirmed by the FDA data re-analysis. Although the influence of cigarette smoking (a 20% increase in clearance values in smokers in comparison to non-smokers)

was found to be statistically significant, this modest increase does not warrant dose adjustment in this population. In the studied population of 128 ALS patients, there were only 19 smokers. Based on this study size, it is difficult to make rational clinical recommendations. In order to make more convincing statement in the label regarding the dose adjustment in smokers, the number of studied smokers in the population would need to be increased.

Comments:

1. The applicant performed NONMEM data analysis using the riluzole plasma data from 128 ALS patients and reported that the data were obtained on two occasions for all patients and on three occasions for 68 patients. The data set submitted for review had the data for 128 patients, where only two patients have plasma riluzole measurements on three occasions.

2. Due to the poor study design (not enough data obtained in the absorption phase), the applicant failed to obtain the realistic estimates of the absorption rate, k_a. The assigning of 5 h^{-1} as a fixed value for k_a was arbitrary. More reliable estimates of k_a should be performed in future studies.

3. The population PK analysis had a certain model miss-specification. Predictions of riluzole plasma concentrations are truncated at high concentrations probably due to the fixing of k_a value. At early time points the model predicts much lower than observed plasma concentration. The choice of a less appropriate model (the one-compartmental model with absorption over the two-compartmental model) may be another reason for the poor fit. Calculation of Akaike criteria for runs 1 and 4 indicates that two-compartmental model should be used for the further development. Literature data suggest the same.

4. The applicant attempted to estimate inter-occasion variability (IOV) for riluzole clearance. In the NONMEM version 4 settings, only up to 10 ETAs could be estimated. Therefore, for the two-compartmental model, random effects of clearance and volumes of distribution could not be estimated together with the estimation of IOV on three occasions. This probably was an additional reason for the development of one-compartmental model. The assumption of the use of the same variance estimate to the several distributions in the IOV model was not properly justified. A more general model applied by the FDA led to the convergence with a better objective function value and similar variabilities on all parameters. Moreover, the 95% confidence intervals calculated for the additional parameters (smoking and genger influences on clearance) were less skewed for the FDA model and included zero value for the smoking factor. Therefore, the parameter estimates obtained with the FDA model are considered to be more reliable.

5. The applicant adequately performed the covariate analysis with evaluation of demographic factors, laboratory data, kidney and liver status, gender and smoking

status. Clearance values were significantly influenced by gender. A typical male patient had 30% higher clearance than a typical female patient. The influence of smoking was statistically significant; however, the FDA model estimated this influence as 20% and applicant's model as 36%. This modest increase does not warrant dose adjustment in this population. In the studied population of 128 ALS patients, there were only 19 smokers.

6. Model validation has not been performed most likely due to the small study size.

Labeling Comments:

Please see the primary reviewer's comments

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics reviewed the Report of the study RP 54274-301 "Population Pharmacokinetics Analysis of Riluzole" and its impact on the changes in the Package Insert. The information regarding the gender differences and the effect of cigarette smoking should be stated in the Package Insert. Please convey the Comments to the applicant.

Elena Mishina Date 8/9/00

Elena Mishina, Ph. D.
Pharmacometrics Specialist

R. Baweja 8/9/00

R. Baweja
Neuropharmacology Team Leader

cc list: NDA 20-599, MehulM, MishinaE, HFD 120
BIOPHARM

APPENDIX 1

Applicant's Results

APPENDIX 2
FDA Results

PREDICTED vs OBSERVED CONCNETRATIONS

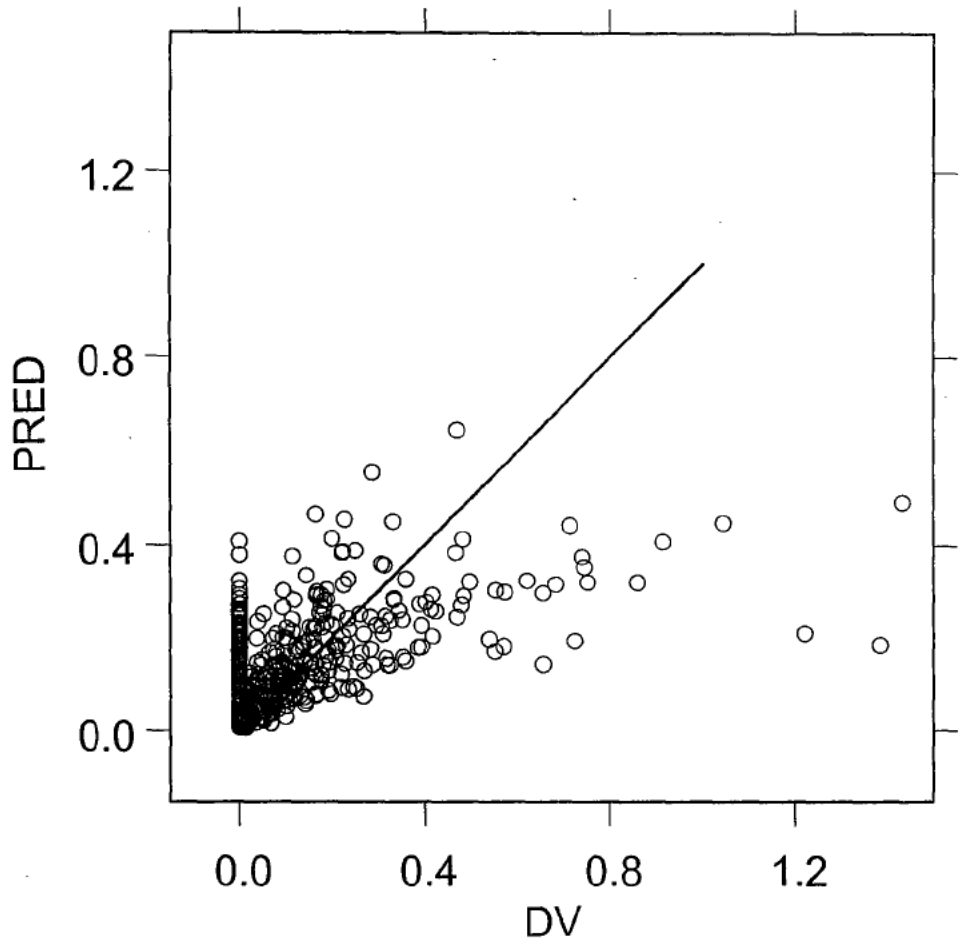


Figure 1

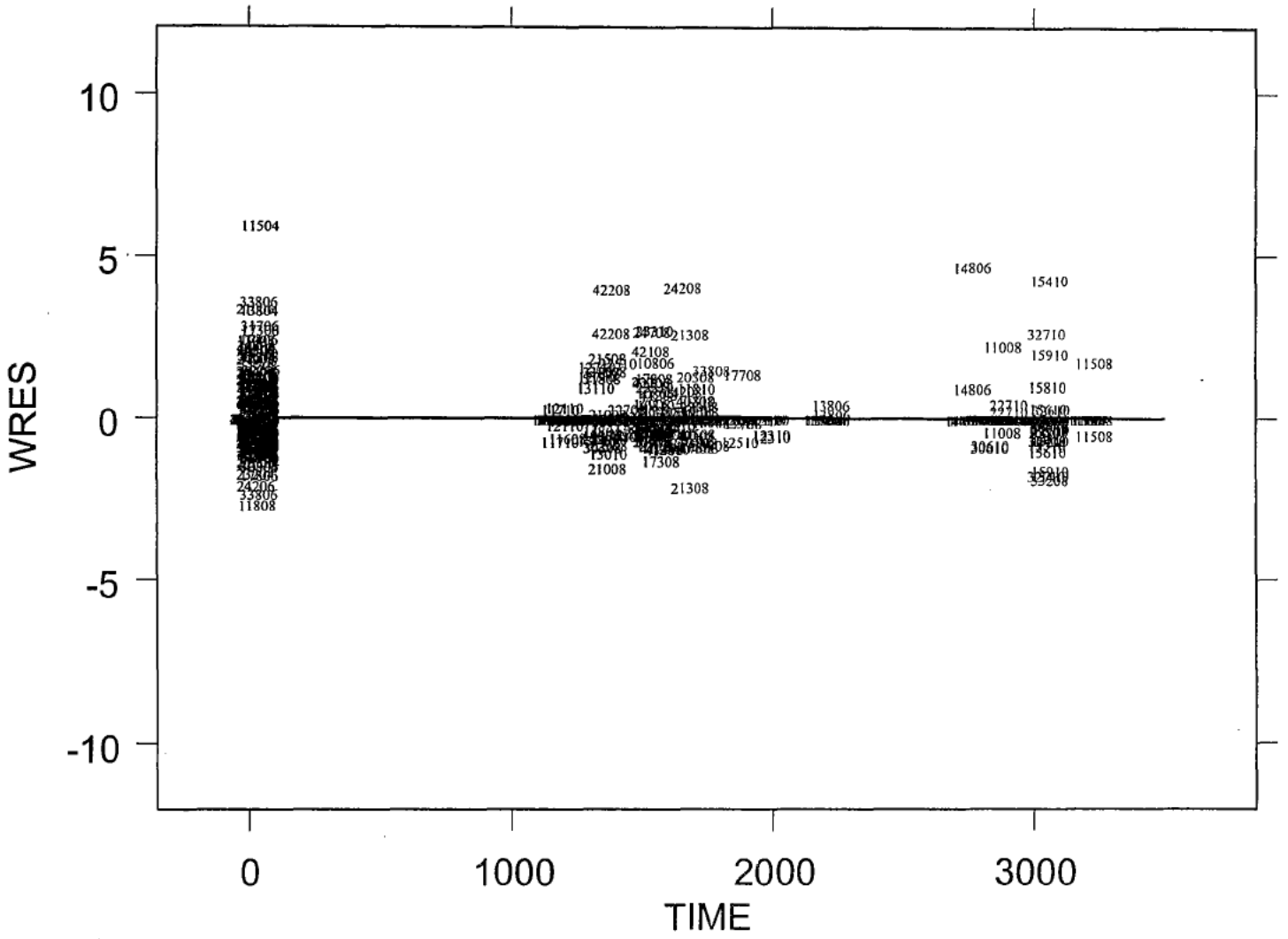


Figure 2

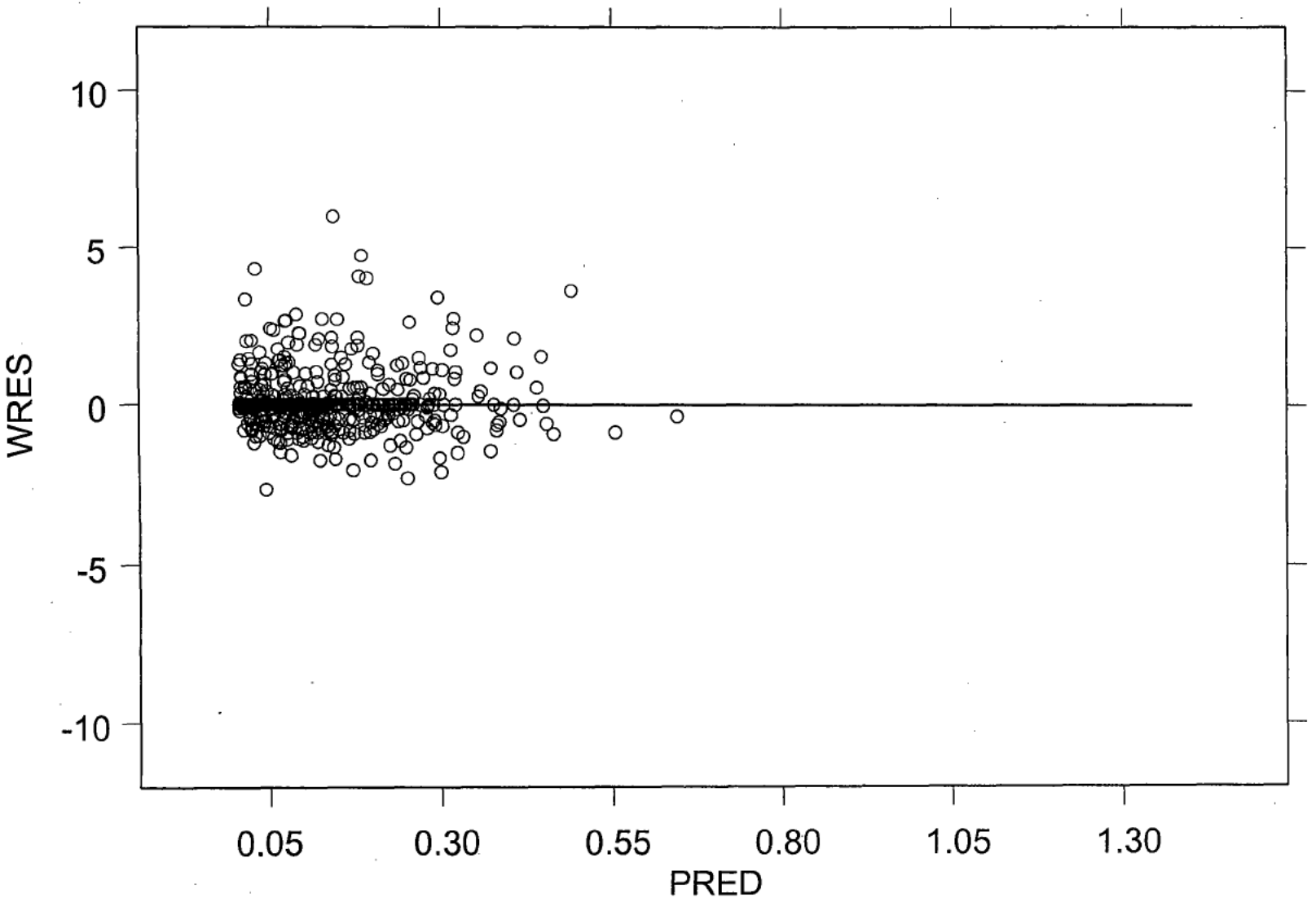

WRES vs PREDICTED CONCENTRATIONS
WRES
10
5
0
-5
-10
0.05
0.30
0.55
0.80
1.05
1.30
PRED

Figure 3

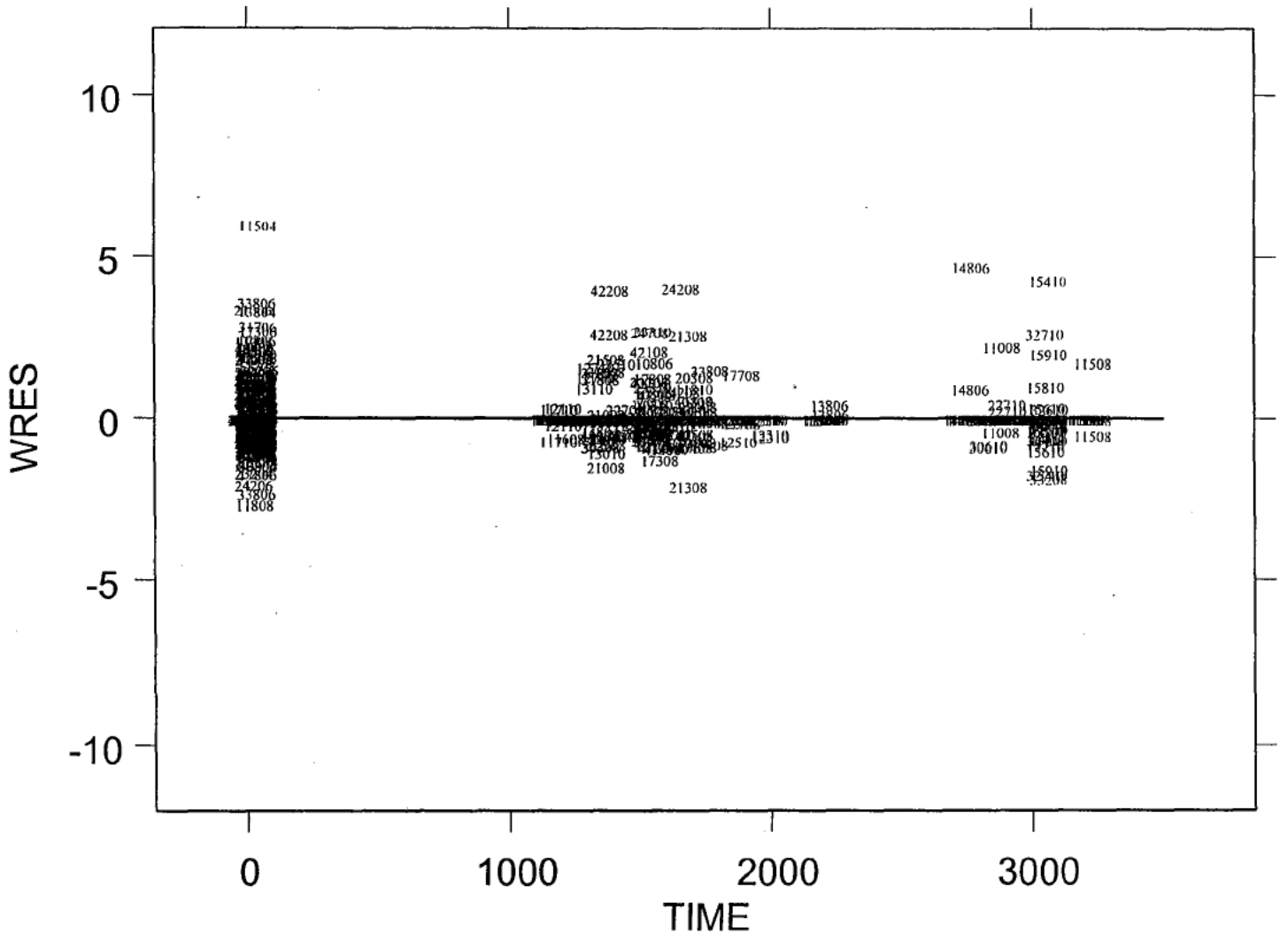


Figure 4

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
Primary review

NDA:	20-599/SLR-002 and SLR-003
Submission Dates:	Sept. 23, 1996; Dec. 23, 1996; Nov. 4, 1998; Dec. 2, 1998; May 9, 2000
Name of Drug:	Rilutek® (riluzole) 50 mg tablets (immediate release, film-coated)
Indication of Drug:	Treatment of amylotropic lateral sclerosis (ALS)
Sponsor:	Aventis (submitted by Rhône-Poulenc Rorer Pharmaceuticals Inc.)
Type of Submission:	Post-approval commitments and labeling revisions
Pharmacokinetic Reviewer:	Maria Sunzel, Ph.D.
Pharmacometrics Reviewer:	Elena Mishina, Ph.D.

Review of post-approval commitments and proposed revision of label for Rilutek® (riluzole) 50 mg tablets (CLINICAL PHARMACOLOGY Subsection).

Rhône-Poulenc Rorer has submitted draft labeling to update pharmacokinetic information for riluzole (Rilutek®) regarding the text for Special Populations (CLINICAL PHARMACOLOGY: Clinical Pharmacokinetics - Special Populations – age, race, renal impairment, hepatic impairment and PRECAUTIONS: Special Populations). The suggested label changes are based on several Phase IV commitments, and a reanalysis of pharmacokinetic data.

The Sponsor has submitted new data regarding:

1. Population pharmacokinetics (PK in patients 09/96; see separate pharmacometrics report)

SLR-002, Submitted 12/23/96:

2. Pharmacokinetics in patients with chronic renal insufficiency (Study Report RP 54274X-164)
3. Pharmacokinetics in patients with chronic liver insufficiency (Study Report RP 54274X-165)
4. Pharmacokinetics in young and elderly, female and male healthy volunteers (Study Report RP 54274X-163)

SLR-003, Submitted 12/22/98:

5. Re-analysis of comparative pharmacokinetics in Japanese and Caucasian subjects. The Sponsor proposes a deletion in the current 'Precautions' section of the label text that states that Japanese subjects have a lower clearance than Caucasian subjects do.

Background

Rilutek® was approved 12/12/95 for treatment of ALS. The recommended dose is 50 mg b.i.d., and the label states that doses higher than the recommended only increases adverse events without any increased clinical benefit. Riluzole (RP54274) is extensively metabolized via hydroxylation (mainly CYP 1A2) and conjugation. Only 2% of a ^{14}C-labelled dose was excreted in urine as unchanged drug, 90% of the total dose was recovered in urine. The plasma protein binding of riluzole is 96%.

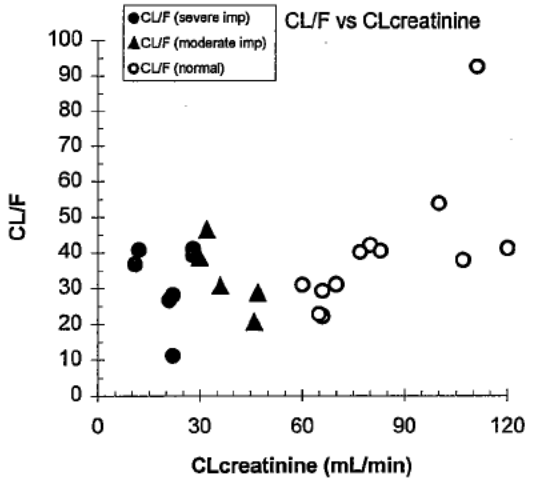
Results SLR-002

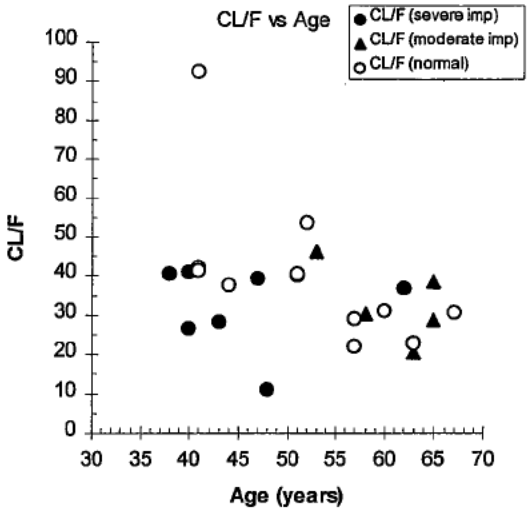
Chronic renal insufficiency:

The influence of renal impairment on the pharmacokinetics of riluzole was adequately studied in patients with moderate ($CL_{creatinine}$=30-50 mL/min/1.73 m^2; n=5; 2F/3M) and severe ($CL_{creatinine}$<30 mL/min/1.73 m^2; n=7; 7M) renal impairment. A control group, matched for gender, age, weight,

had normal renal function (n=12; 2F/10M). All subjects were given a single oral dose of 50 mg riluzole.

As shown in the graphs below, age and degree of renal impairment did not influence the oral clearance of riluzole. The pharmacokinetic parameters of riluzole for the different groups were similar, see Appendix 1. Therefore, from a pharmacokinetic point of view, special dosing recommendations are not necessary for patients with various degrees of renal impairment.

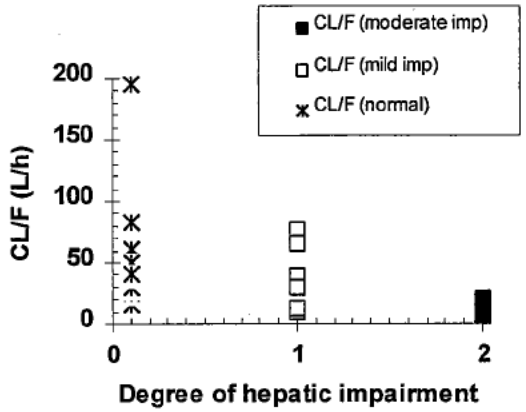


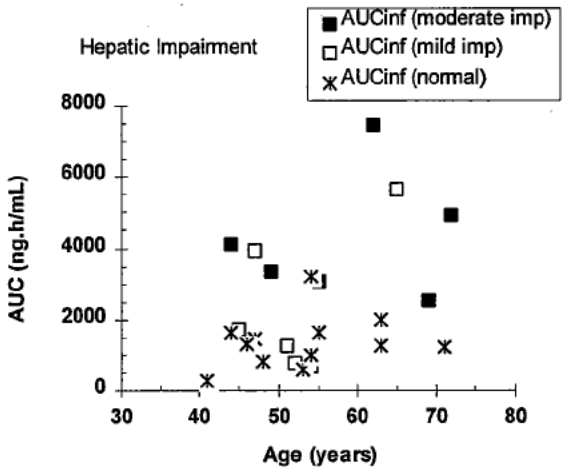


Chronic hepatic insufficiency:

The influence of hepatic impairment on the pharmacokinetics of riluzole was adequately studied in patients with mild (Child Pugh's Score A; n=6; 2F/4M) and moderate (Child- Pugh's Score B; n=6; 1F/5M) hepatic impairment. A control group, matched for gender, age, weight, had normal hepatic function (n=12; 3F/9M). The pharmacokinetics of riluzole has not been studied in patients with severe hepatic impairment. All subjects were given a single oral dose of 50 mg riluzole.

As shown in the figures below, age and degree of hepatic impairment (1=mild impairment; 2=moderate impairment) influenced the oral clearance and AUC of riluzole.





The AUC showed a 1.7-fold increase in the patients with mild impairment, and a 3-fold increase in the patients with moderate hepatic impairment compared to the matched healthy control group.

The oral clearance (CL/F) decreased 1.4-fold in patients with mild impairment compared to healthy subjects, and a corresponding 4-fold decrease in CL/F was observed in patients with moderate liver impairment. The changes in AUC and CL/F were statistically significant only in the comparison between the moderately hepatically impaired patients and healthy subjects. The terminal t½ of riluzole was similar in patients with mild (19±7 h) and moderate (24±13 h) hepatic impairment and healthy subjects (25±7 h). The pharmacokinetic parameters of riluzole for the different groups are shown in Appendix 1. The degree of plasma protein binding was not measured in the study. The lack of t½ prolongation in subjects with hepatic impairment compared to healthy volunteers is not easily explainable. Theoretically, it could be attributable to a corresponding decrease in volume of distribution, or more likely, an increase in the absolute bioavailability of riluzole, which is 60% in healthy subjects. Based on the study results, from a pharmacokinetic point of view, special dosing recommendations are recommended for patients with chronic mild and moderate hepatic impairment (Child Pugh's Scores A and B).

Age and gender

The influence of age and gender on the pharmacokinetics of riluzole was adequately studied in young and elderly, male and female, healthy volunteers. 18 elderly (9F/9M; 74.6±0.9 yrs, range 70-82 yrs) and 18 young (9F/9M; 21.4.6±0.7 yrs, range 18-30 yrs) volunteers participated in the study. Each young volunteer was matched to one elderly according to gender and weight. All subjects were given repeated daily oral doses of 100 mg riluzole (50 mg b.i.d.) during four days. On Day 5 a 50 mg dose was administered in the morning, and blood samples were collected 72 h post-dose.

The pharmacokinetics of riluzole was similar in both elderly and young volunteers, as shown in the table below. The pharmacokinetics of riluzole was also similar between male and female volunteers, as shown in Appendix 1.

Table 13 : Comparison of pharmacokinetic parameters between elderly and young volunteers

Parameter	Elderly volunteers	Young volunteers	Statistical tests*
Cmax $ng.ml^{-1}$	271 +/- 122	244 +/- 140	NS
AUC $ng.h.ml^{-1}$	2566 +/- 1001	2252 +/- 1162	NS
AUC(0-72h) $ng.h.ml^{-1}$	2074 +/- 851	1721 +/- 878	NS
t1/2 h	40.30 +/- 8.84	49.03 +/- 10.93	S (Prob> |T| = 0.0149)
Clss/F $L.h^{-1}$	57.1 +/- 25.2	70.1 +/- 30.3	NS

* : NS = No significant difference, S = Significant difference

The terminal half-life (t½) determined after repeated riluzole dosing was longer than that after single doses from the two studies investigating hepatic and renal impairment. The same bioanalytical method and laboratory was used for the plasma analyses (LC/MS/MS; LOQ 0.5 ng/mL), and the post-dose sampling period was between 72 and 96 h in all three studies. Steady state was reached within 2-3 days, indicating that an 'effective' t½ is somewhat shorter. Therefore, although the terminal t½ is approximately 10 hours longer after repeated dosing compared to single doses, and the discrepancy between the doses does not influence predictions of time to reach steady state by using a shorter t½.

There the pharmacokinetics of riluzole was similar between female and male volunteers irrespective of age. However, the oral clearance in female patients was approximately 30% lower compared to male patients, as described in the pharmacometrics report and the revised label text.

From a pharmacokinetic point of view, special dosing recommendations are not necessary for elderly patients.

Results SLR-003

Pharmacokinetics in Japanese subjects

The Sponsor has provided a reanalysis of pharmacokinetic data submitted in the original NDA. Two separate studies with repeated escalating doses of similar design were performed in Japanese subjects (Study AG 157) and Caucasian subjects (Study AG 158). Both studies had a parallel group design, with 25, 50 and 100 mg b.i.d. dosing, and pharmacokinetic parameters were calculated after a single dose (Day 1, 48 h wash-out) and at steady state. In the new analysis the Sponsor has weight and dose normalized the AUC and C_{max} parameters of the Japanese and Caucasian subjects. The dose was normalized to 50 mg, and the average weight to 70.65 kg by combining both studies (Japanese 62.5±5.55 kg; Caucasians 78.8±9.96 kg). The sponsor also suggests that the analysis should only be performed on the single dose data (Day 1).

No statistically significant differences from the single dose data were found between the two populations after this adjustment, based on single dose data.

The rationale the Sponsor gives is the following: "*However, the terminal elimination half-life increases on repeated dosing and thus AUC, C_{max} and C_{min} increase more than would be predicted based upon the single dose pharmacokinetics of Rilutek. For example, the mean ratio $AUC_{(0\text{-}12,Day\ 13)}/AUC_{(0\text{-}inf,\ Day1)}$ was 1.69 at the 50 mg bid dosage. Consequently, the steady-state pharmacokinetics of Rilutek is not predictable from the single dose data on Day 1 using a noncompartmental approach (if predictable, the AUC ratio above would be near 1.0). Because the pharmacokinetics of Rilutek are not predictable at steady-state based upon single dose data, with significantly more accumulation than would be predicted, a Japanese vs. Caucasian comparison of oral clearance (CL/F) derived from the AUC determined over a dosing interval (0-12hr) at steady-steady on Day 13 is not a reliable comparative measure for this pharmacokinetic parameter. In fact, the most appropriate data for comparing the pharmacokinetics of Rilutek between Japanese and Caucasian subjects is the weight and dose normalized pharmacokinetic data obtained on Day 1 in these studies. In addition, there are inconsistencies in the data on Day 13 as it relates to comparing pharmacokinetic parameters between Japanese and Caucasian subjects.*"

The explanation given by the Sponsor shows some discrepancy with the remainder of the data submitted for the label changes. Steady state data would be more reliable for the analysis, especially in light of the improved bioanalytical method, where the limit of quantitation (LOQ) has been lowered from 5 ng/mL (used in Studies 157 and 158) to 0.5 ng/mL. The reported t½ for normal healthy volunteers after a single dose (Studies 164 and 165) was on average 24-30 hours using the more sensitive bioanalytical method (LOQ 0.5 ng/mL), whereas it was calculated to 5-6 h for both the Japanese and Caucasian subjects (LOQ 5 ng/mL), in the two earlier studies. The calculations of total AUC (0-infinity) will be underestimated by using a short underestimated t½. Therefore, steady state data using the AUC calculated for one dosing interval should be a more reliable estimate. In the statistical analysis submitted in 1998, the $AUC_{(0\text{-}12h,Day\ 13)}$ at steady state normalized for both weight and dose, was statistically significant between the two populations.

Unfortunately, the Sponsor does not give a further explanation to what the inconsistencies in the steady state data (Day 13) are between the Japanese and Caucasian subjects, that would make any comparison at steady state potentially unreliable.

In the original NDA review (9/27/95), concerns regarding the metabolic data from the two studies were raised. According to the original review the two populations showed dissimilarities in metabolism and clearance, also after the above mentioned correction for body weight (but not dose):

"In both Japanese and Caucasian subjects, <2% of unchanged riluzole is recovered in the urine. However, in Japanese subjects only 15-20% of the administered dose is recovered in the urine as a major glucuronide metabolite as compared to about 40% in Caucasians. This would suggest some differences in the qualitative and quantitative role of the different metabolic pathways involved in the metabolism of riluzole."
"In Caucasian subjects, the kinetics of riluzole is linear over the single dose range of 25-300 mg and over the multiple dose range of 25-100 mg given every 12 hours. In Japanese subjects the kinetics of riluzole is linear over the single dose range of 25-200 mg, and over the multiple dose range of 25-100 mg given every 12 hours, both C_{max} and AUC appear to reach a plateau at higher doses."
"Comparison of the pharmacokinetics between Japanese and Caucasians at the proposed labeled dosing regimen of 50 mg given every 12 hours, suggest that on an average Japanese subjects have higher C_{max} and AUC values (47 % and 60 % increase, respectively) and a corresponding decrease in apparent systemic clearance, Cl/F, of 50% when normalized for dose and body weight as compared to Caucasians. A statistically significant difference between both studies was found for C_{max}, $AUC_{(0\text{-}12\ h)}$, Cl/F and Vd/F obtained at steady-state."

Since the Sponsor has not provided any explanation for the dissimilarities between the two populations regarding dose linearity or addressed the difference in glucuronide formation, from a pharmacokinetic point of view, the current label text should be kept.

Comments on label revisions (see Appendix 2, Pages 10-11 for revisions proposed by the sponsor):

1. Renal Impairment: The label changes are acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. Please revise the proposed sentence according to the following minor changes (number of subjects included):

   "There is no significant difference in pharmacokinetic parameters between patients with moderate (n= 5; creatinine clearance 30-50 $ml.min^{-1}$) and severe (n= 7; creatinine clearance < 30 $ml.min^{-1}$) renal insufficiency and healthy volunteers (n= 12) after a single oral dose of 50 mg riluzole."

   Also, please include the following phrase in the sections CLINICAL PHARMACOLOGY, Pharmacokinetics, *Special Populations* and WARNINGS, PRECAUTIONS, *Special Populations*:

   "The pharmacokinetics of riluzole has not been studied in patients undergoing hemodialysis."

2. Hepatic Impairment: The label changes are acceptable to the Office of Clinical Pharmacology and Biopharmaceutics. Please revise the proposed sentence according to the following minor changes (number of subjects and severity of liver impairment included):

   "The area-under-the-curve (AUC) of riluzole, after a single 50 mg oral dose increases by about 1.7-fold in patients with mild chronic liver insufficiency (n= 6; Child Pugh's score A) and by about 3-fold in patients with moderate chronic liver insufficiency (n= 6; Child Pugh's score B) compared to healthy volunteers (n= 12) (see WARNINGS and PRECAUTIONS)."

   Also, please include the following phrase in the sections CLINICAL PHARMACOLOGY, Pharmacokinetics, *Special Populations* and WARNINGS, PRECAUTIONS, *Special Populations*:

   "The pharmacokinetics of riluzole has not been studied in patients with severe hepatic impairment."

3. Age: All label changes are acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

4. Gender: The suggested revisions regarding "CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations" is acceptable for 'gender', except for a minor change in the following sentence:
"However, in one placebo-controlled clinical trial with population pharmacokinetics, riluzole mean clearance was found to be 30% (b) (4) lower in female patients (corresponding to an approximate increase in AUC of 45% (b) (4) as compared to male patients."

5. Smoking: The suggested revisions regarding "CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations" should be replaced by the following sentences:
"Patients who smoke cigarettes eliminate riluzole 20% (b) (4) faster than non-smoking patients, based on a population pharmacokinetic analysis on data from 128 ALS patients, of whom 19 were smokers. However, there is no need for dosage adjustment in these patients."

6. Race: From a pharmacokinetic point of view, the current (unrevised) label text for 'Race' should not be changed.

   The reason for keeping the unrevised text regarding race is as follows: The explanation given by the Sponsor to only use single dose data for a comparison between Japanese and Caucasian subjects, shows some discrepancy with the remainder of the data submitted for the label changes. Steady state data would be more reliable for the analysis, especially in light of the improved bioanalytical method, where the limit of quantitation (LOQ) has been lowered from 5 ng/mL (used in Studies 157 and 158) to 0.5 ng/mL. The reported t½ for normal healthy volunteers after a single dose (Studies 164 and 165) was on average 24-30 hours using the more sensitive bioanalytical method (LOQ 0.5 ng/mL), whereas it was calculated to 5-6 h for both Japanese and Caucasian subjects (LOQ 5 ng/mL). The calculations of total $AUC_{(0\text{-inf})}$ will be underestimated by using a much shorter t½. Therefore, steady state data using the AUC calculated for one dosing interval should be a much more reliable estimate. In the statistical analysis submitted 1998, the steady state $AUC_{(0\text{-}12h,Day\ 13)}$ normalized for both weight and dose, was statistically significant between the two populations.

   Unfortunately, the Sponsor does not give a further explanation to what the inconsistencies in the steady state data (Day 13) are between the Japanese and Caucasian subjects, that would make any comparison at steady state potentially unreliable.

   In the original NDA review, concerns regarding the metabolic data from the two studies were raised. According to the original review the two populations also showed dissimilarities in metabolic patterns: "In both Japanese and Caucasian subjects, <2% of unchanged riluzole is recovered in the urine. However, in Japanese subjects only 15-20% of the administered dose is recovered in the urine as a major glucuronide metabolite as compared to about 40% in Caucasians. This would suggest some differences in the qualitative and quantitative role of the different metabolic pathways involved in the metabolism of riluzole."

   Age, Gender, cont.: PRECAUTIONS, Special populations, 2nd sentence. Please keep the following, slightly altered, statement: 'Also, female patients and Japanese patients may possess a lower metabolic capacity to eliminate riluzole compared to males and Caucasian subjects, respectively (see CLINICAL PHARMACOLOGY: Special populations).

Recommendation:

The submitted study reports fulfil the Phase IV commitments by the sponsor. The submitted data also partly support the proposed label changes.
The label changes for Rilutek® (riluzole) 50 mg tablets are acceptable to the Office of Clinical Pharmacology and Biopharmaceutics after the suggested corrections of the proposed label have been made. Please convey the 'Comments on label revisions' to the sponsor.

Maria Sunzel, Ph.D. Maria Sunzel 8/9/00

Elena Mishina, Ph.D. Elena Mishina 8/9/00

RD/FT Initialed by Ray Baweja, Ph.D. R. Baweja 8/9/00.

cc: NDA 20-599, HFD-120, HFD-860 (Mehta, Baweja, Mishina, Sunzel), Central Document Room (Biopharm File)

Appendix 1

PHARMACOKINETIC PARAMETERS

Chronic renal insufficiency (Study Report RP 54274X-164)

Pharmacokinetic results :

Volunteers with chronic renal insufficiency (n = 12 : 10 males and 2 females)

Volunteers	Tmax * h	Cmax ng.ml^{-1}	AUC(0-96h) ng.h.ml^{-1}	AUC ng.h.ml^{-1}	t1/2 h	CL/F L.h^{-1}
Severe R.I. n = 7	0.50 (0.50 - 1.25**)	243 +/- 65 CV = 27%	1770 +/- 1113 CV = 63%	1895 +/- 1187 CV = 63%	30.51 +/- 6.16 CV = 20%	31.9 +/- 10.9 CV = 34
Moderate R.I. n = 5	0.75 (0.50 - 1.50)	320 +/- 110 CV = 35%	1578 +/- 468 CV = 30%	1645 +/- 525 CV = 32%	25.48 +/- 6.00 CV = 24%	32.9 +/- 9.9 CV = 30%
All volunteers n = 12	0.63 (0.50 - 1.50)*	275 +/- 91 CV = 33	1690 +/- 875 CV = 52%	1791 +/- 941 CV = 53	28.41 +/- 6.36 CV = 22%	32.3 +/- 10.0 CV = 31%

*: median, **: range

Healthy volunteers (n = 12 : 10 males and 2 females)

volunteers	Tmax h	Cmax ng.ml^{-1}	AUC(0-96h) ng.h.ml^{-1}	AUC ng.h.ml^{-1}	t1/2 h	CL/F L.h^{-1}
Healthy	0.75 (0.50-1.50)*	275 +/- 107 CV = 39%	1339 +/- 487 CV = 36%	1421 +/- 489 CV = 34%	32.39 +/- 10.76 CV = 33%	40.4 +/- 18.7 CV = 46%

*: median, **: range

No statistically significant difference was found between the three groups of subjects (moderate, severe renal impaired and healthy volunteers). The pharmacokinetic profile of riluzole is similar between renal-impaired volunteers and healthy volunteers.

Chronic hepatic insufficiency (Study Report RP 54274X-165)

Pharmacokinetic Results: Mean pharmacokinetic parameters of RP54274

		Cmax (ng.ml^{-1})	*tmax* (h)	*AUC(0-t)* (ng.h.ml^{-1})	*AUC* (ng.h.ml^{-1})	*t1/2λz* (h)	*CL/F* (l.h^{-1})
Healthy Subjects	mean	264	-	1315	1364	24.6	53.7
	sd	129	-	734	751	6.8	47.8
	CV%	49	-	56	55	28	89
	median	229	0.88	1230	1283	24.8	39.0
	min	77	0.50	244	257	13.7	15.6
	max	483	3.00	3142	3199	34.9	194.7
	n	12	12	12	12	12	12
		Cmax (ng.ml^{-1})	*tmax* (h)	*AUC(0-t)* (ng.h.ml^{-1})	*AUC* (ng.h.ml^{-1})	*t1/2λz* (h)	*CL/F* (l.h^{-1})
Patients with Child Pugh's score A	mean	323	-	2284	2327	19.1	38.8
	sd	95	-	1993	2026	6.6	27.6
	CV%	29	-	87	87	34	71
	median	311	0.50	1445	1478	15.9	34.6
	min	202	0.25	632	656	13.6	8.8
	max	485	4.00	5553	5672	28.4	76.2
	n	6	6	6	6	6	6
Patients with Child Pugh's score B	mean	298	-	3817	4232	23.9	13.4
	sd	108	-	1188	1786	13.0	4.7
	CV%	36	-	31	42	55	35
	median	271	1.25	3663	3729	16.8	13.5
	min	195	0.50	2485	2513	14.6	6.7
	max	486	2.00	5855	7451	46.6	19.9
	n	6	6	6	6	6	6

No statistically significant difference was shown between the healthy subjects and the mild hepatic impaired patientsin terms of AUC and CL/F But, the increase of AUC in moderate hepatic impaired patients(Child Pugh's score B) was statistically significant when compared to healthy subjects. The decrease of CL/F in moderate hepatic impaired patients (Child Pugh's score B) was statistically significant when compared to healthy subjects.

Age and gender (Study Report RP 54274X-163) **Appendix 1 cont.**

Table 10 : Mean pharmacokinetic parameters (elderly volunteers)

Gender		Tmax h	Cmax $ng.ml^{-1}$	AUC(0-72h) $ng.h.ml^{-1}$	AUC(0-12h) $ng.h.ml^{-1}$	CLss/F $l.h^{-1}$	t1/2 h	AUC $ng.h.ml^{-1}$
Male	Mean		280	2027	1009	53.8	42.08	2515
	SD		95	707	299	17.0	11.31	782
	CV%		34	35	30	32	27	31
	Median	0.75 (0.50-1.50)*						
	n	9	9	9	9	9	9	9
Female	Mean		262	2121	1049	60.3	38.52	2617
	SD		149	1017	502	32.2	5.55	1230
	CV%		57	48	48	53	14	47
	Median	0.75 (0.50-3.00)*						
	n	9	9	9	9	9	9	9

* : range of Tmax

Table 11 : Mean pharmacokinetic parameters (young volunteers)

Gender		Tmax h	Cmax $ng.ml^{-1}$	AUC(0-72h) $ng.h.ml^{-1}$	AUC(0-12h) $ng.h.ml^{-1}$	CLss/F $l.h^{-1}$	t1/2 h	AUC $ng.h.ml^{-1}$
Male	Mean		200	1778	858	68.8	49.33	2368
	SD		103	787	433	26.5	11.08	1133
	CV%		52	44	50	39	22	48
	Median	0.75 0.50-3.00)*						
	n	9	9	9	9	9	7	7
Female	Mean		289	1664	880	71.4	48.8	2161
	SD		163	1006	522	35.3	11.49	1244
	CV%		57	60	59	49	24	58
	Median	0.50 (0.50-1.25)*						
	n	9	9	9	9	9	9	9

* : range of Tmax

THE SPONSOR HAS SUGGESTED THE FOLLOWING CHANGES TO THE CURRENTLY APPROVED LABEL:

CLINICAL PHARMACOLOGY, Pharmacokinetics, *Special Populations*:

~~The pharmacokinetics of riluzole have not been studied in renally and hepatically impaired subjects, nor is there information about the effects of smoking, age and gender on the pharmacokinetics of riluzole but certain differences in population subsets should be anticipated (see PRECAUTIONS).~~

Hepatic ~~and Renal~~ Disease: ~~Since riluzole is extensively metabolized and subsequently excreted in the urine, it is likely that functional hepatic and renal impairment will reduce the clearance of riluzole and its metabolites and give higher plasma levels (see PRECAUTIONS and WARNINGS).~~ The area-under-the-curve (AUC) of riluzole, after a single 50 mg oral dose increases by about 1.7-fold in patients with mild chronic liver insufficiency and by about 3-fold in patients with moderate chronic liver insufficiency (see WARNINGS and PRECAUTIONS).

Renal Disease: There is no significant difference in pharmacokinetic parameters between patients with moderate and severe renal insufficiency (creatinine clearance between 10 and 50 $ml.min^{-1}$) and healthy volunteers after a single oral dose of 50 mg riluzole.

Age: ~~Age related decreased renal function would be expected to give higher plasma levels of riluzole and metabolites. However, in controlled clinical trials, in which approximately 30% of patients were over 65, there were no differences in adverse events between younger and older patients (see PRECAUTIONS).~~ The pharmacokinetic parameters of riluzole after multiple dose administration (4.5 days of treatment at 50 mg riluzole b.i.d.) are not ~~a~~ffected in the elderly (≥70 years).

Gender: ~~CYP 1A2 activity has been reported to be lower in women than in men. Therefore, a gender effect on riluzole kinetics may be expected in women, resulting in higher blood concentrations of riluzole and its metabolites (see PRECAUTIONS).~~ No gender effect on riluzole pharmacokinetics has been found in young or elderly healthy subjects. However, in one placebo-controlled clinical trial with population pharmacokinetics, riluzole mean clearance was found to be (b) (4) lower in female patients (corresponding to an approximate increase in AUC of (b) (4)) as compared to male patients. No ~~gender effect on~~ favorable or adverse effects of riluzole in relation to gender were ~~was~~ seen in controlled trials, however.

Smoking: ~~Cigarette smoking is known to induce CYP 1A2.~~ Patients who smoke cigarettes ~~would be expected to~~ eliminate riluzole (b) (4) faster than non-smoking patients, which is consistent with the known induction of CYP 1A2 in smoking patients. There is no information, however, on the effect of, or need for, dosage adjustment in these patients.

Race: ~~Clearance of riluzole in Japanese subjects native to Japan was found to be 50% lower as compared to Caucasians after normalizing for body weight. Although it is not clear if this difference is due to genetic or environmental factors (*e.g.*, smoking, alcohol, coffee, and dietary preferences), it is possible that Japanese subjects may possess a lower capacity (oxidative and/or conjugative) for metabolizing riluzole. There are no studies, however, of lower doses in Japanese subjects (see PRECAUTIONS).~~

Appendix 2 cont.

PRECAUTIONS

Use in Patients with Concomitant Disease

RILUTEK should be used with caution in patients with concomitant liver ~~and/or renal~~ insufficiency (see WARNINGS, CLINICAL PHARMACOLOGY). In particular, in cases of RILUTEK-induced hepatic injury manifested by elevated liver enzymes, the effect of the hepatic injury on RILUTEK metabolism is unknown.

Special Populations

Riluzole should be used with caution in elderly patients whose hepatic ~~or renal~~ functions may be compromised due to age. ~~Also, females and Japanese patients may possess a lower metabolic capacity to eliminate riluzole compared to males and Caucasian subjects, respectively (see CLINICAL PHARMACOLOGY: Special populations)~~.

DOSAGE AND ADMINISTRATION

The recommended dose for RILUTEK is 50 mg every 12 hours. No increased benefit can be expected from higher daily doses, but adverse events are increased.
RILUTEK tablets should be taken at least an hour before, or two hours after, a meal to avoid a food-related decrease in bioavailability.

Special Populations

Patients with Impaired ~~Renal or~~ Hepatic Function: ~~Studies have not yet been completed in these populations~~ (see WARNINGS, PRECAUTIONS, CLINICAL PHARMACOLOGY).

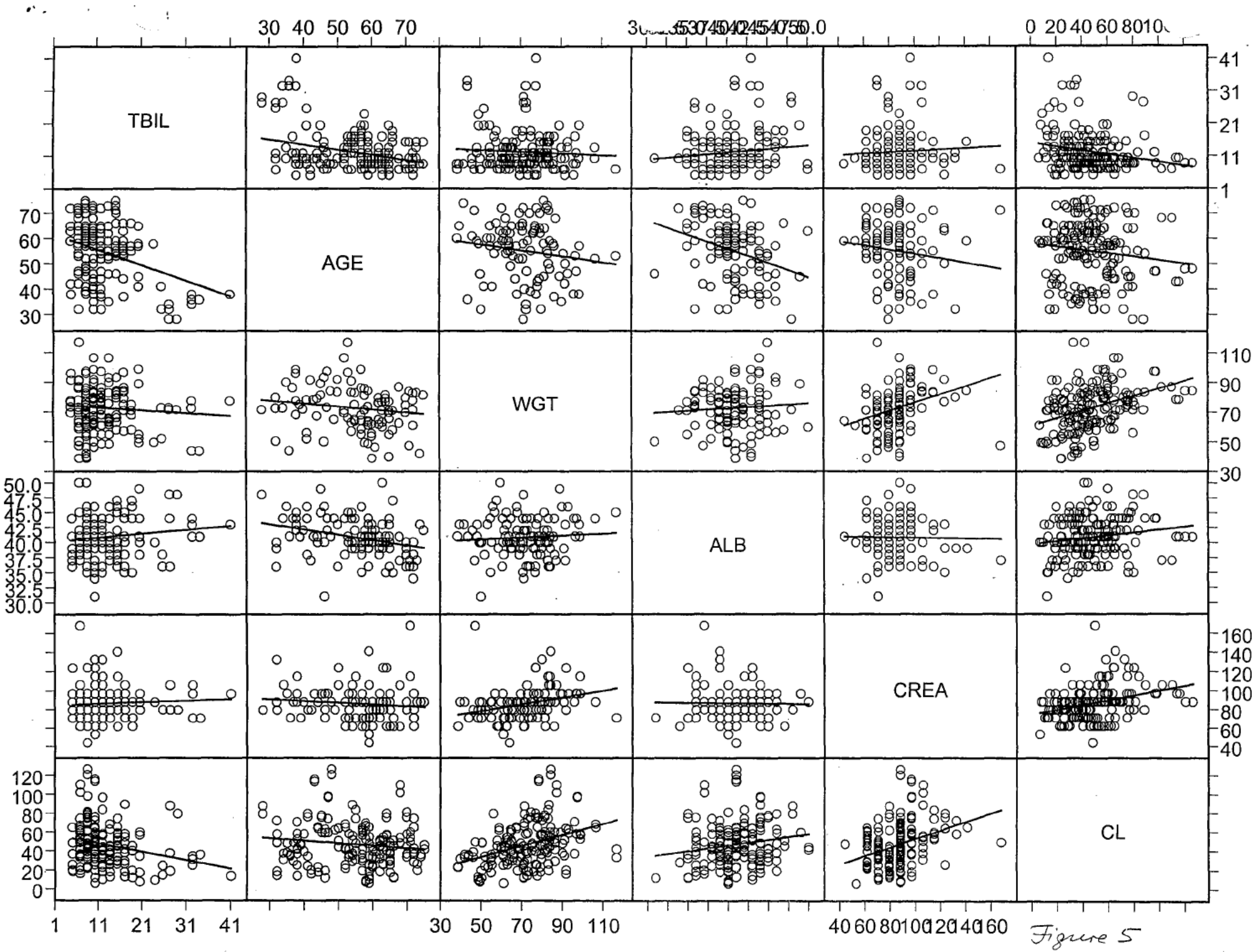


Figure 5

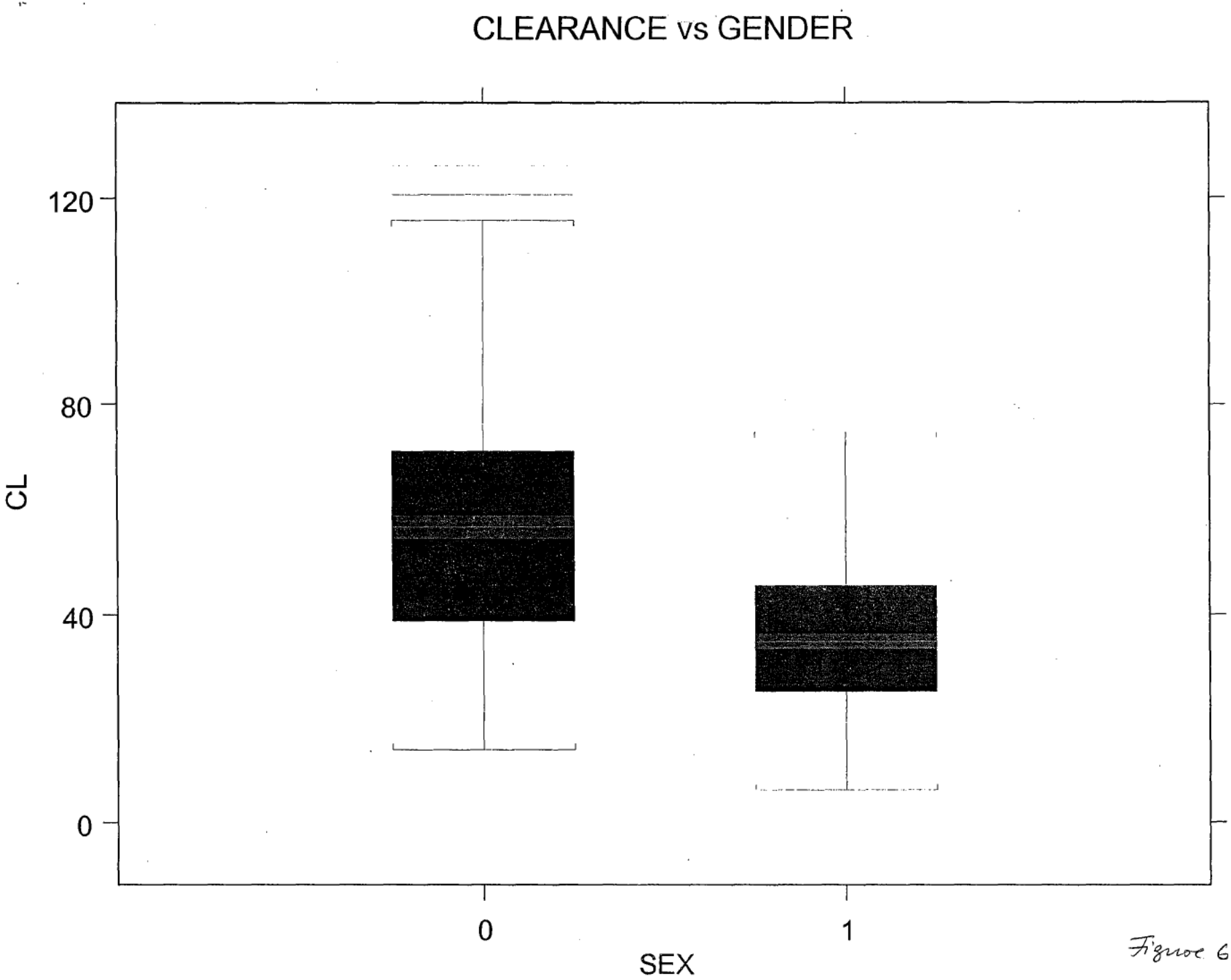


Figure 6

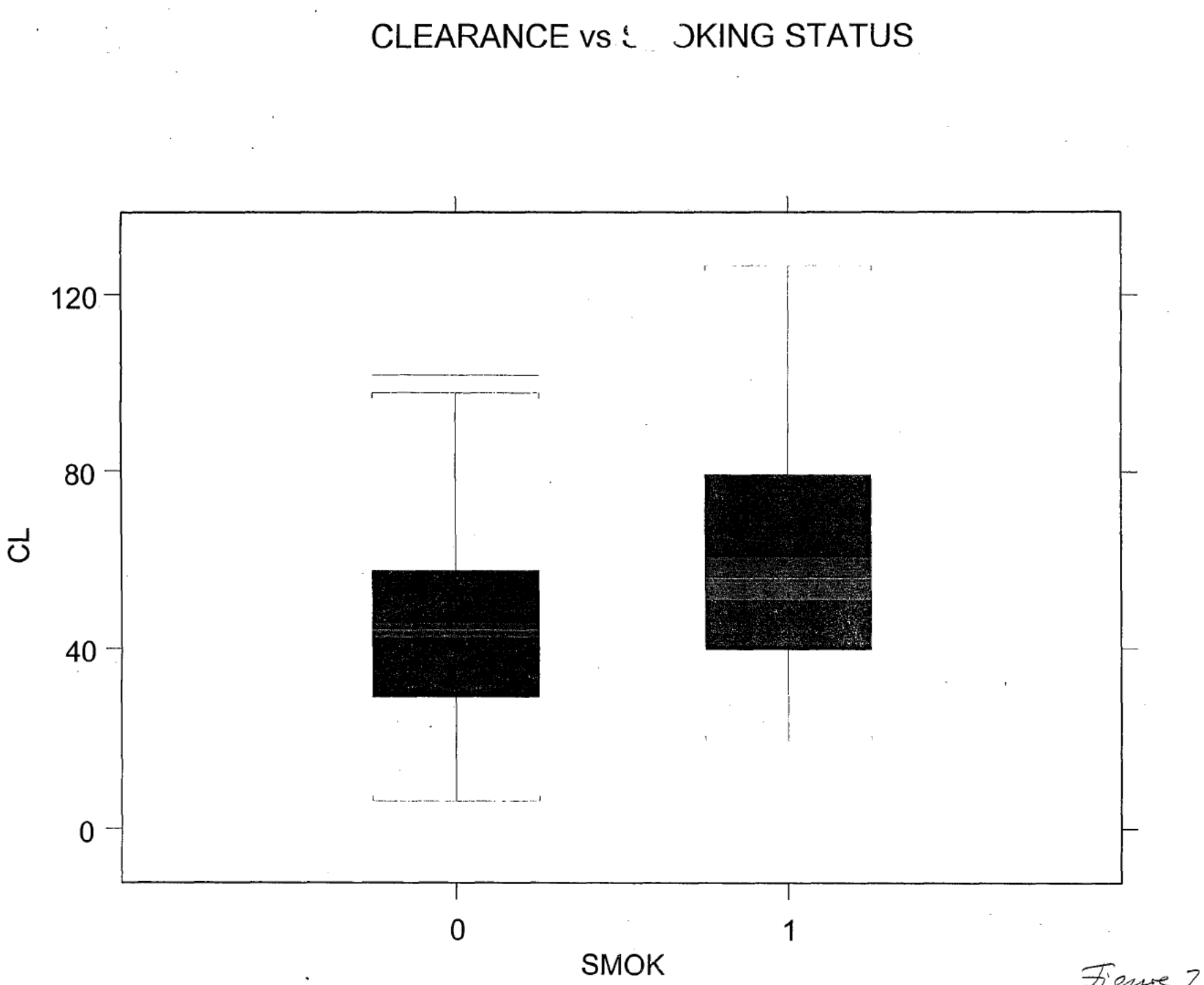


Figure 7

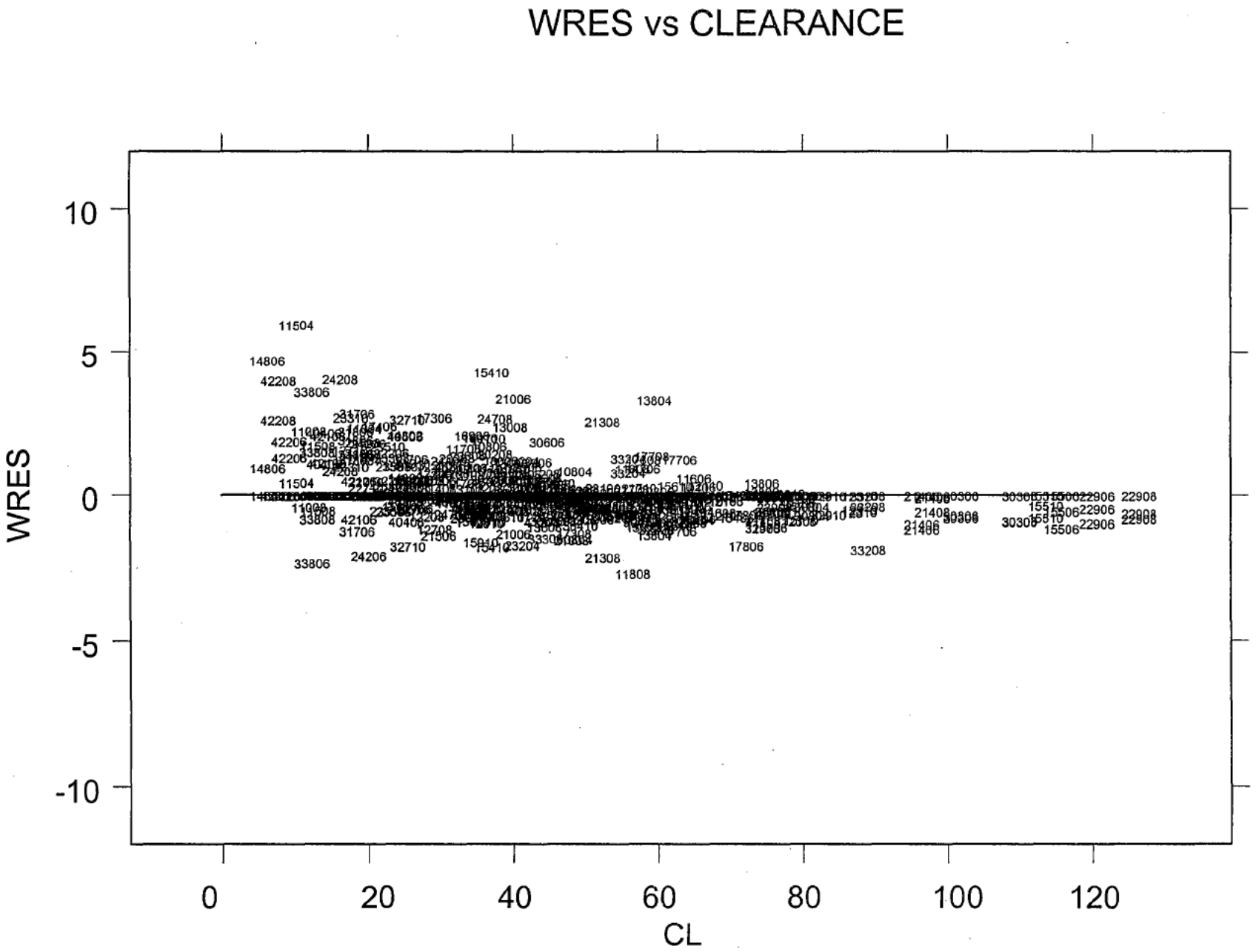


Figure 8

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-599/S002

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER
LABELING REVIEW

Date: May 14, 2003
Drug: Rilutek (riluzole) 50 mg Tablets
NDA: 20-599
Sponsor: Aventis Pharmaceuticals
Indication: Amyotrophic Lateral Sclerosis (ALS)
Supplements:

NDA	Supplement	Dated	Action
Rilutek (riluzole) 50 mg Tablets (NDA 20-599)			
20-599	SLR-002	12-24-96; amended on 11-4-98, and 4-24-03	AE Action Letter Dated 9-6-00; Complete Response to AE Letter Received on 4-24-03; **Open Supplement**
20-599	SLR-003	12-22-98 and amended on 4-24-03	AE Action Letter Dated 9-6-00; Complete Response to AE Letter Received on 4-24-03; **Open Supplement**
20-599	SLR-005	8-17-99; amended on 3-22-00, 12-8-00, 3-9-01, and 4-24-03	AE Action Letter Dated 12-18-02; Complete Response to AE Letter Received on 4-24-03; **Open Supplement**
20-599	SLR-006	11-3-99	AP Letter 4-10-00

Notes of Interest

- The last approved labeling supplement was SLR-006. The sponsor submitted FPL in this CBE supplement, and it was found to be acceptable.

SUPPLEMENT REVIEW

20-599/SLR-002
Date: 12-24-96; amended on 11-4-98, and 4-24-03
CBE: No
Label Code: N/A, draft labeling
Reviewed by Medical Officer/OCPB: Yes, approvable

This supplement provides for revisions to the **CLINICAL PHARMACOLOGY-Pharmacokinetics-Special Populations** subsection to describe the special population effects of age, renal impairment and hepatic impairment on the tolerability and pharmacokinetics of riluzole.

20-599/SLR-003
Date: 12-22-98 and amended on 4-24-03
CBE: No
Label Code: N/A, draft labeling
Reviewed by Medical Officer/OCPB: Yes, approvable

This supplement provides for revisions to the **CLINICAL PHARMACOLOGY-Pharmacokinetics-Special Populations** subsection to revise the statement which indicates a difference in clearance between Japanese and Caucasian subjects.

20-599/SLR-005
Date: 8-17-99; amended on 3-22-00, 12-8-00, 3-9-01, and 4-24-03
CBE: No
Label Code: 50069093
Reviewed by Pharmacologist: Yes, approvable

This supplement provides for revisions to the **PRECAUTIONS-Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection based upon the results of two carcinogenicity studies.

LABELING REVIEW

Changes to the FPL, submitted on 4-24-03 (Label Code: 50069093), when compared to the last approved FPL, submitted on 11-3-99 (Label Code: IN5336B), that are not noted in the above supplements:

1. At the start of the labeling, the statement "Caution: federal law prohibits dispensing without a prescription" was changed to "Rx only". This was reported in the 5-12-01 annual report.

2. At the end of the labeling, the sponsor has changed the manufacturing site. This was reported in a CBE chemistry supplement submitted on 12-20-02 (SCM-007).

3. In the PRECAUTIONS section, the subsection heading **Use in the Elderly** has been revised to **Geriatric Use**.

CONCLUSIONS

1. The sponsor has responded to all of the above open labeling supplements in a submission dated 4-24-03. They have submitted FPL which incorporates the requested labeling revisions contained in our 2 AE letters dated 9-6-00 and 12-18-02.

2. I have compared the FPL submitted on 4-24-03 with the last approved FPL, submitted on 11-3-99, and the only labeling changes were the ones requested in the 2 aforementioned AE action letters as well as the minor revisions listed above.

3. Therefore, I recommend that we approve all 3 supplements. I also recommend that only the Clinical Team Leader needs to concur with this action since the sponsor has done exactly what we have requested.

{See appended electronic signature page}
Paul David, R.Ph., Senior Regulatory Project Manager

{See appended electronic signature page}
Robbin Nighswander, R.Ph.,
Supervisory Regulatory Health Officer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul David
5/14/03 09:51:31 AM
CSO

Robbin Nighswander
5/14/03 09:52:31 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-599/S002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Aventis Pharmaceuticals Inc.	March 7, 2003
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(816) 966-5100	(816) 966-6794
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Headquarters: 200 Crossing Boulevard Bridgewater, NJ 08807-0890 (908) 243-6000 Site: 10236 Marion Park Drive P.O. Box 9720 Kansas City, MO 64134-0720	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 20-599

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	
Riluzole	Rilutek Tablet	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		**CODE NAME** *(If any)*
2-amino-6-(trifluoromethoxy)benzothiazole		RP-54274
DOSAGE FORM:	**STRENGTHS:**	**ROUTE OF ADMINISTRATION:**
Tablet	50 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:

For the treatment of patients with amyotrophic lateral sclerosis (ALS). Riluzole extends survival and/or time to tracheostomy.

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☒ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

Response to FDA Approvable letters dated September 6, 2000 and December 18, 2002 (S-002, S-003, and S-005)

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☒	2. Labeling *(check one)* ☐ Draft Labeling ☒ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	Kerry Rothschild, J.D., Director, Regulatory Affairs	March 7, 2003

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
200 Crossing Boulevard, Bridgewater, NJ 08807-0890, Mailstop: BX2-209G	(908) 231-2848

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date JAN 14 1997

NDA No. 20-599

Rhone-Poulene Rorer
500 Arcola Road
Collegeville, PA 19426-0107

Attention: Thomas E. Donnelly Jr.

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: **RILUTEK-TABLETS**

NDA Number: 20-599

Supplement Number: S-002

Date of Supplement: DECEMBER 24, 1996

Date of Receipt: DECEMBER 26, 1996

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on FEBUARY 24, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacologic Drug Products
Attention: Document Control Room
5600 Fishers Lane, HFD-120
Rockville, MD 20857

Sincerely yours,

Katherine H. Higgins

(FOR) John Purvis

Chief, Project Management Staff
Division of Neuropharmacologic Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

FORM FDA 3217b (11/95)

★ U.S. GPO: 1995-404-897/20714

13.1

USER FEE DATA ENTRY/VALIDATION FORM Ver.2(9/1/93)

NDA # 20-599 DOCUMENT ID/LETTER DATE SLR-002/12-24-96

APPLICANT NAME Rhone-Poulenc RORER

PRODUCT NAME Riluteк (Riluzole) Tablets

FORM MUST BE COMPLETED BY (10 DAYS FROM DOCUMENT RECEIPT): 1-3-97

1. YES (NO) **CLINICAL DATA?**
[Check YES if contains study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials. "Clinical data" do not include data used to modify the labelling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).]

REF **IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION?**

IF SUPPLEMENT and NO CLINICAL DATA INCLUDED, SKIP TO ITEM 11!

2. YES NO **505(b)(2) NDA?** An application in which one or more of the pivotal studies (rather than all) was not conducted or sponsored by the applicant and the applicant does not have a right of reference to that study. In addition, the firm must have made a patent certification under section 505(b)(2)(A) and (B) of the Act and must have cited a reference listed drug on which it is basing its application.

YES NO **If 505(b)(2) NDA - FEE APPLIES?**
[Check YES if application is for a new chemical entity or Indication. Check NO if application is for a previously approved drug substance or indication.]

3. YES NO **LARGE VOLUME PARENTERAL APPROVED BEFORE 9/1/92?** [Check YES only if a supplement with clinical data submitted to an LVP application first approved before 9/1/92.]

4. YES NO **505(j) NDA?** Abbreviated Application **IF YES, SKIP TO ITEM 11!**

5. YES NO **506 NDA?** Insulin Product **IF YES, SKIP TO ITEM 11!**

6. YES NO **NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE** (OTHER THAN BUNDLING)? IF YES, list ALL NDA numbers, review divisions & indicate those for which application fees apply.

NDA #	DIVISION		
N_____	_____	FEE	NO FEE
N_____	_____	FEE	NO FEE

7. YES NO **BUNDLING POLICY APPLIED CORRECTLY?** NO DATA ENTRY REQUIRED FOR ELEMENT
[Check YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Check NO if application should be split into more than one application or submitted as an original instead of a supplement. IF NO, list resulting NDA numbers, and review divisions.]

NDA #	DIVISION	NDA #	DIVISION
N_____	_____	N_____	_____

8. YES NO **SMALL BUSINESS EXCEPTION GRANTED?** [Check YES only if the NDA contains a copy of a written notice from the FDA Waiver Officer that a exception has been granted.]

9. YES NO **WAIVER GRANTED?** [Check YES only if the NDA contains a copy of a written notice from the FDA Waiver Officer that a waiver has been granted.]

10. YES NO **PRIORITY SUBMISSION?** [Check YES if Priority. Check NO if Standard.]

Katureah H. Higgs 1/7/97 John S. Lewis 1/7/97

11. CSO SIGNATURE/DATE SCSO CONCURRENCE SIGNATURE/DATE

COPY DISTRIBUTION: ORIGINAL TO ARCHIVAL AFTER DATA ENTRY, ONE COPY EACH TO DIVISION FILE AND CDER, ASSOCIATE DIRECTOR FOR POLICY HFD-1-1

DA 1-14-97