Clinical trials of riluzole in patients with ALS

R.G. Miller, MD; J.P. Bouchard, MD; P. Duquette, MD; A. Eisen, MD; D. Gelinas, MD; Y. Harati, MD; T.L. Munsat, MD; L. Powe, MD; J. Rothstein, MD; P. Salzman, PhD; R.L. Sufit, MD; and the ALS/Riluzole Study Group-II*

Article abstract—Two double-blinded, placebo-controlled clinical trials of riluzole have now been carried out in more than 1,100 patients with ALS. The results of both studies show a modest benefit in prolonging survival that is statistically significant. These results led to the availability of this drug by the Food and Drug Administration for use in the United States beginning in early 1996. This is the first drug that has been available for ALS. It begins a new era in both basic and clinical research in an attempt to find a cure for this disease.

NEUROLOGY 1996;47(Suppl 2):S86–S92

ALS is a disorder characterized by relentlessly progressive weakness caused by degeneration of both upper and lower motor neurons. A large number of clinical trials have been carried out in this disease. Until recently all have been negative, including more than a dozen controlled trials in the last 15 years with more than 2,500 patients.

Although the cause of ALS is still unknown, an emerging consensus suggests that excitotoxic damage to motor neurons may play an important role.[1,2] In brief, evidence from a number of experimental models suggests that glutamate excitotoxicity can damage motor neurons and that excessive concentrations of glutamate are present in the blood and CSF of many patients with ALS.[3-6] Glutamate transport is selectively impaired in motor control areas of the brain and spinal cord in ALS patients because of a defect in transport proteins.[7-9] Riluzole inhibits the presynaptic release of glutamate and reduces neuronal damage in a number of experimental models.[10-13] It was reasoned that the anti-glutamate properties of riluzole might be beneficial in patients with ALS, and clinical trials were undertaken.

The first trial was stratified, double-blinded, and placebo-controlled.[14] Patients were stratified according to whether the onset of their disease was in the bulbar musculature (e.g., dysarthria, dysphagia) or in the limb muscles. The study involved 155 patients with 77 assigned to receive riluzole 100 mg/day and 78 placebo. These results were published in early 1994, and the findings will be only very briefly summarized here. The main outcome measure was tracheostomy-free survival. Of 77 patients taking riluzole, 38 were alive at the end of the trial compared with 29 of 78 taking placebo. These differences were statistically significant; however, a number of questions were raised because the prolonged survival in patients taking riluzole was substantially greater for patients with bulbar onset disease, and the number of bulbar patients was small. The survival of all riluzole-treated patients taken together was significantly longer than patients taking placebo. Nonetheless, in order to address these and other concerns, a larger trial was undertaken.

Phase III study design. The design of the larger trial was similar to the first with the addition of a dose-ranging design and a longer period of evaluation.[15] The study was stratified according to bulbar or limb onset, and the design was double-blind and placebo-controlled. Tracheostomy-free survival was again chosen as the primary outcome measure. Broad entry criteria were utilized in an attempt to obtain a representative population of ALS patients, as was true in the first study. An independent safety board was constituted and carried out external safety review throughout the trial, with an interim

*See Appendix on page 90 for the participating institutions and principal investigators.

From the Department of Neurology (Drs. Miller and Gelinas), California Pacific Medical Center, San Francisco, CA; the Department of Neurological Sciences (Dr. Bouchard), Hôspital de L'Enfant-Jesus, Quebec City, Canada; the Department of Neurology (Dr. Duquette), Hôspital Notre-Dame, Montreal, Canada; the Neuromuscular Disease Unit (Dr. Eisen), Vancouver Hospital and Health Science Center, Vancouver, Canada; the Department of Neurology (Dr. Harati), Baylor College of Medicine, Houston, TX; the Department of Neurology (Dr. Munsat), New England Medical Center, Boston, MA; Rhone-Poulenc Rorer (Drs. Powe and Salzman), Antony, France and Collegeville, PA locations, respectively; the Department of Neurology (Dr. Rothstein), Johns Hopkins School of Medicine, Baltimore, MD; and the Department of Neurology (Dr. Sufit), Northwestern University Medical School, Chicago, IL.

Supported by Rhône-Poulenc Rorer. The investigators received no financial incentives such as equity interest, patent rights, or corporate affiliation. Compensation was provided only for the costs of the study and for partial reimbursement of investigator time in carrying out the trial.

Address correspondence and reprint requests to Dr. Robert G. Miller, Department of Neurology, California Pacific Medical Center, 2324 Sacramento Street, #150, San Francisco, CA 94115.

Table 1 Clinical and demographic features

	Placebo	R 100*
Number	242	236
Male/Female (%)	63/37	61/39
Age (yrs)†	56 ± 12	57 ± 11
Caucasian (%)	98.3	97.9
Weight (kg)†	68 ± 13	68 ± 13
Form of ALS at onset		
Bulbar	31%	30%
Limb	69%	70%
Sporadic	95%	96%
Familial	5%	4%
Duration of disease (yrs)	1.8	1.7
Vital capacity (% predicted)†	88 ± 18	88 ± 19

* Patients taking riluzole 100 mg/d.
† Mean ± SD.

efficacy analysis. Secondary end points included manual muscle testing, a modified Norris scale for evaluating bulbar and limb function, the clinical global impression scale, and visual analogue scales for stiffness, cramps, fasciculations, and fatigability.

The statistical analysis was based upon intent to treat and included all randomized patients. Comparisons were adjusted only for bulbar versus limb onset utilizing the log rank analysis as the primary method. The Wilcoxon method was also used as it more fully accounts for early events. In addition, the Cox proportional hazard model was utilized to adjust for factors that correlate with survival[16] (age, gender, duration of disease, body weight, respiratory function at entry, time since diagnosis). Thus, survival was analyzed using three different methods, with the Cox model providing a multivariate approach. The secondary outcome measures were evaluated using analysis of variance. Enrollment for this study began in December 1992 and continued until November 1993. Enrollment began in European countries and later in North America. Thirty-one sites were involved, with 5 in the United States, 3 in Canada, and the remainder in France and other European countries. An interim analysis was carried out in October 1994, and the study was terminated on December 31, 1994. Additional analysis was carried out including the first 12 months of survival data for all patients taking riluzole.

Results. There were no significant differences in the demographic characteristics of patients taking placebo compared with those taking riluzole for gender, age, race, or body weight (table 1). Clinical characteristics at baseline were also not significantly different between patients taking riluzole and those taking placebo. There were no differences between treatment groups in terms of the number of patients with bulbar versus limb onset, sporadic versus familial disease, duration of disease, or vital capacity at entry.

Nine hundred fifty-nine patients were enrolled in this study and randomized. Of 236 patients taking 100 mg riluzole, 134 were alive at the end of the trial (of whom 21 prematurely discontinued treatment during the study), and of 242 placebo-treated patients, 122 were alive at the end of the study (of whom 14 discontinued). The Kaplan-Meier survival

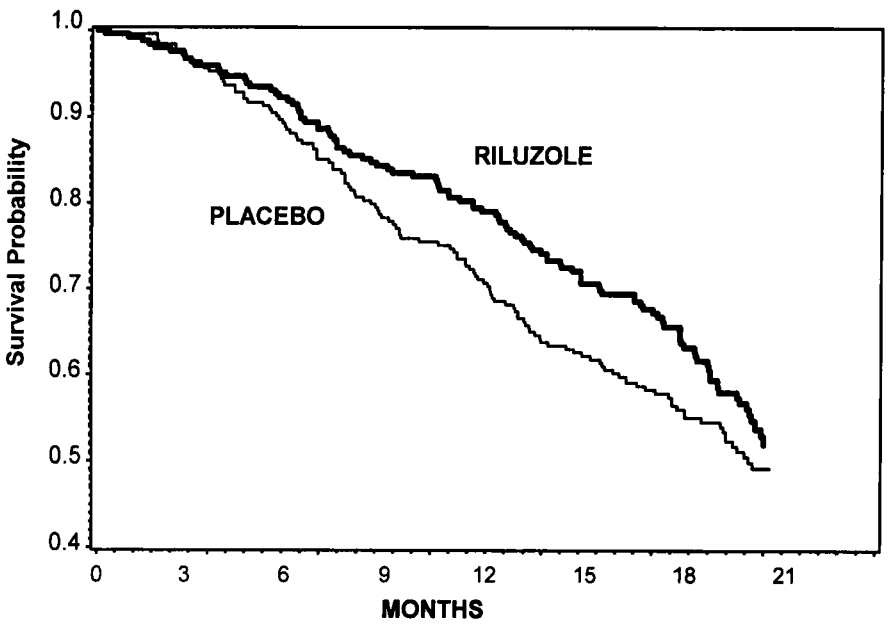

Figure 1. Kaplan-Meier plots of survival for patients with ALS receiving placebo (n = 242) or riluzole 100 mg daily (n = 238).

Table 2 Most frequent clinical adverse experiences

COSTART term	Placebo (%) (N = 320)	Riluzole (%) (N = 794)
Asthenia	12	18
Nausea	11	16
Lung function decrease	10	13
Accidental injury	11	12
Dizziness	3	7
Abdominal pain	4	6
Hypertension	4	5
Diarrhea	3	6
Pneumonia	4	6
Anorexia	4	5
Vomiting	2	4
Vertigo	1	3
Somnolence	1	2
Circumoral paresthesia	0	2

Combined data from both the first and second trials are shown.

curves demonstrated prolonged survival for patients taking 100 mg riluzole compared with placebo (figure 1). A separation in the curves began after a few months and increased throughout the study, albeit with less separation in the last few months of the study. Utilizing two-sided p values, the log rank analysis demonstrated significantly prolonged survival at 9 ($p = 0.03$), 12 ($p = 0.01$), and 15 ($p = 0.02$) months for patients taking riluzole 100 mg compared with placebo. At the end of the trial, the survival rate was 50.4% for placebo-treated patients and 56.8% for patients taking riluzole 100 mg/day. This difference corresponds to a p value of 0.076 utilizing the log rank test and a p value of 0.05 with the Wilcoxon. These values correspond to a relative increase in the probability of survival for patients taking riluzole 100 mg/day that ranged between 1 and 18% during each 3-month interval within the study. The relative increase in survival probability was 4% for riluzole-treated patients between 3 and 6 months, 11% between 6 and 9 months, 17% between 9 and 12 months, 18% between 12 and 15 months, and 8% between 15 and 18 months. The Kaplan-Meier survival curves for the four treatment groups (placebo, riluzole 50 mg/d, riluzole 100 mg/d, riluzole 200 mg/d) showed an apparent dose relationship. When the trend test was applied to the analysis of these four curves, there was a dose-response relationship that is significant ($p = 0.04$), indicating that the pattern of survival for all three groups taken together is significantly better than placebo. Using the Cox model of analysis, the improved survival for patients treated with riluzole was significant at all dose levels (50 mg, $p = 0.044$; 100 mg, $p = 0.002$; 200 mg, $p = 0.0004$). The actual survival rates were 50.4% for placebo, 55.3% for 50 mg, 56.8% for 100 mg, and 57.8% for 200 mg.

Two additional survival analyses were undertaken on patients who received a full year of treatment with riluzole 100 mg/day. The survival rate was 62.8% for placebo-treated patients and 73.7% for patients receiving riluzole 100 mg/day ($p = 0.019$, using the log rank analysis). When patients with tracheostomy or tracheal intubation were excluded from the analysis and death was the only end point, the survival rates in patients treated for 1 year were 52.1% in the placebo group and 62% in the group

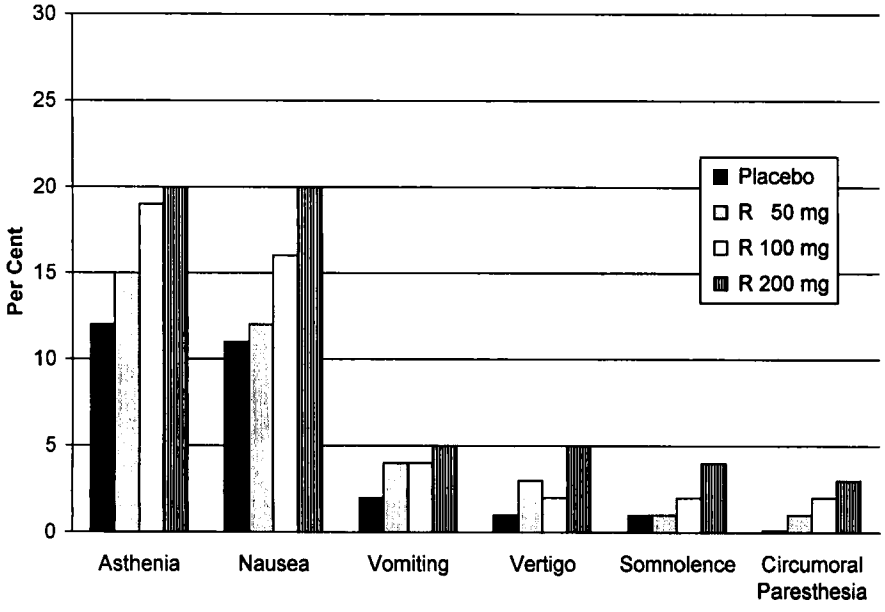

Figure 2. Adverse experiences that appeared to reflect a dose relationship in patients with ALS taking riluzole.

Table 3 *Liver function test elevations (percent of patients)*

Laboratory parameter	Maximum value*	Placebo	R 50 mg	R 100 mg	R 200 mg
ALT	>3N but ≤5N	2	5	7	12
	>5N	2	1	3	3
AST	>3N but ≤5N	1	1	4	1
	>5N	1	0	0.3	1

Combined data from both the first and second trials are shown.

* >3N = more than 3 times the upper limit of normal; >5N = more than 5 times the upper limit of normal.

ALT = serum glutamic-pyruvic transaminase (SGPT); AST = Serum glutamic-oxaloacetic transaminase (SGOT).

treated with riluzole 100 mg/day (p = 0.029, log rank).

Secondary end points, such as manual muscle testing, Norris scores, clinical global impression, and visual analogue scales, were not significantly different between the placebo group and patients receiving riluzole. It is not clear why no benefit was observed in any of the secondary end points. It is possible that the instruments were too imprecise. Certainly manual muscle testing is a technique that has many disadvantages, including nonlinearity and substantial variability among examiners. The same is true of functional scales where substantial validation and standardization are necessary. In future trials, quantitative isometric strength measures might provide a better assessment tool.

Safety. A variety of adverse experiences appeared in the large trial (table 2). Riluzole was generally well tolerated. Approximately 90% of all patients reported adverse experiences whether receiving riluzole or placebo. Many of the adverse experiences are associated with ALS (e.g., asthenia, lung function decrease, and accidental injury). Dose-related adverse experiences included asthenia, nausea, vomiting, vertigo, somnolence, and circumoral paresthesia (figure 2). From a clinical perspective, most of the adverse experiences that were dose-related resolved with dose reduction. Frequently, after 1 to 2 weeks the earlier dose could be resumed and was well tolerated. The overall rate of discontinuation from the study because of adverse experiences was 11% in patients receiving placebo and 14% with riluzole (all doses combined).

Liver function abnormalities occurred in many patients. The elevation of liver function tests was dose related (table 3). Many patients had elevation of liver function tests, but only 3% of patients exceeded five times the upper limit of normal. Two percent of placebo patients showed such elevations. Patients who exceeded five times the upper limit of normal were taken off riluzole and did not receive the drug again. Their liver function generally returned to baseline within a few months. Although marked elevations of liver function tests were relatively uncommon, a modest increase in liver enzymes was quite common and in some ways similar to that observed in patients taking carbamazepine[17] or azathioprine.[18] It is recommended that patients starting riluzole have liver function test monitoring monthly for the first 3 months, every 3 months for the next year, and periodically thereafter.

In summary, there was a statistically significant, albeit modest benefit in survival for patients taking riluzole compared with placebo in this trial. These results confirm and extend those of a previous smaller trial. Thus, two placebo-controlled, double-blinded studies have shown a beneficial impact upon the progress of ALS in over 1,100 patients. The drug has been safe and generally well tolerated. The recommended dose is 50 mg bid, and regular monitoring of liver function must be undertaken.

The availability of riluzole is an important small first step in our progress toward finding a cure for ALS. It provides hope for patients and their families who are battling this disease. It provides new directions for research since the positive results lend support to the hypothesis that glutamate excitotoxicity is an important mechanism in ALS. In the future, clinical trials involving combinations of riluzole with neurotrophic factors and anti-oxidants, as well as other anti-glutamate compounds, should be strongly considered.

Appendix. *ALS/Riluzole Study Group-II: Steering Committee: Chairman: P. Guillet (Rhône-Poulenc Rorer, Antony, France). G. Bensimon (Pr. A.J. Puech, Dept. of Pharmacology, Hôpital de la Pitie-Salpetriere, Paris, France); J.C. Delumeau (Rhône-Poulenc Rorer, Antony, France); S. Durrleman (Rhône-Poulenc Rorer, Antony, France); L. Lacomblez (Pr. A.J. Puech, Dept. of Pharmacology, Hôpital de la Pitie-Salpetriere, Paris, France); P.N. Leigh (Dept. of Neu-*

rology, Institute of Psychiatry De Crespigny Park, London, UK); V. Meininger (Dept. of Pharmacology, Hôpital de la Pitie-Salpetriere, Paris, France); L. Powe (Rhône-Poulenc Rorer, Antony, France).

Investigators and Coinvestigators at each center: Belgium: J.M. Maloteaux, C. Delwaide (E.C. Laterre, Universite de Louvain, Brussels). Canada: J.P. Bouchard (Hôpital de l'Enfant-Jesus, Quebec City); P. Duquette, M. Girard, C. Masse (Hôpital Notre-Dame, Montreal); A. Eisen (Vancouver Hospital and Health Science Centre, Vancouver). France: O. Blin, J.P. Azulay, F. Bille-Turc, J. Pouget (G. Serratrice, Hôpital de la Timone, Marseilles); P. Bouche (P. Bouche, Hôpital de la Pitie-Salpetriere, Paris); W. Camu, B. Carlander (M. Billiard, Hôpital G. de Chauliac, Montpellier); M. Clanet, G. Angibaud, M.C. Arne-Bes, M. Benazet (M. Clanet, Hôpital Purpan, Toulouse); P. Couratier (J.M. Vallat, Hôpital Dupuytren, Limoges); C. Desnuelle (M. Chatel, Hôpital Pasteur, Nice); A. Lagueny, E. Ellie (J. Julien, Hôpital Haut-Leveque, Pessac); V. Meininger, M. Dib, A. Rozier, F. Salachas (P. Brunet, Hôpital de la Pitie-Salpetriere, Paris); F. Viader, D. Delaunay (B. Lechevalier, C.H.U. de la Côte de Nacre, Caen). Germany: R. Dengler, G. Kuther, M. Troger (Medizinische Hochschule, Hannover); A. Ludolph, R. Bachus, C. Gericke (Neurologische Universitatsklinik, Charite, Berlin); H. Przuntek, M. Langkafel (St. Josef-Hospital, Bochum); K. Schimrigk, W.H. Jost, J. Osterhage, J. Prudlo (Neurologische Universitatsklinik, Hamburg). Spain: J. Mora, D. Chaverri, E. Saenz (Institude de Salud Carlos III, Madrid). United Kingdom: D. Jefferson, V. Orpe (Queen Medical Centre, Nottingham); R.J.M. Lane, R.W. Orrell (Charing Cross Hospital, London); P.N. Leigh, C.M. Lloyd, T. Barbie (Institute of Psychiatry, London); J.D. Mitchell, J. Kilshaw (Royal Preston Hospital, Preston); H.S. Pall, M. Goodwin (Queen Elizabeth Hospital, Birmingham); W. Schady, S. Duncan, C. Moore, C. Rickards (Manchester Royal Infirmary, Manchester); P.J. Shaw, G. Chari, B. Pickering (Queen Victoria Infirmary, Newcastle-upon-Tyne); M. Swash (The Royal London Hospital, London). USA: Y. Harati, C.L. Gooch, C.W. Echols (Baylor College of Medicine and VAMC, Houston); R.G. Miller, D.F. Gelinas, A. Quien (California Pacific Medical Center, San Francisco); T.L. Munsat, B. Thornell (New England Medical Center, Boston); J.D. Rothstein, L. Clawson (The Johns Hopkins School of Medicine, Baltimore); R. Sufit, P. Casey (Northwestern University Medical School, Chicago).

References

1. Rothman SM, Thurston JH, Hauhart RE. Delayed neurotoxicity of excitatory amino acids in vitro. Neuroscience 1987;22: 471–480.
2. Choi DW. Glutamate neurotoxicity and disease of the nervous system. Neuron 1988;1:623–634.
3. Plaitakis A, Caroscio JT. Abnormal glutamate metabolism in ALS [abstract]. Ann Neurol 1985;18:165.
4. Plaitakis A, Caroscio JT. Abnormal glutamate metabolism in amyotrophic lateral sclerosis. Ann Neurol 1987;22:575–579.
5. Perry TL, Hansen S, Jones K. Brain glutamate deficiency in amyotrophic lateral sclerosis. Neurology 1987;37:1845–1848.
6. Plaitakis A, Constantakakis E, Smith J. The neuroexcitotoxic amino acids glutamate and aspartate are altered in the spinal cord and brain in amyotrophic lateral sclerosis. Ann Neurol 1988;24:446–449.
7. Rothstein JD, Martin LJ, Kuncl RW. Decreased glutamate transport by the brain and spinal cord in amyotrophic lateral sclerosis. N Engl J Med 1992;326:1464–1468.
8. Rothstein J, Van Kammen M, Levey AI, Martin LJ, Kuncl RW. Selective loss of glial glutamate transporter GLT-1 in amyotrophic lateral sclerosis. Ann Neurol 1995;38:73–84.
9. Rothstein JD, Jin L, Dykes-Hoberg M, Kuncl RW. Chronic glutamate uptake inhibition produces a model of slow neurotoxicity. Proc Natl Acad Sci USA 1993;90:6591–6595.
10. Estevez AG, Stutzmann JM, Barbeito L. Protective effect of riluzole on excitatory amino acid-mediated neurotoxicity on motoneuron-enriched cultures. Eur J Pharmacol 1995;280:47–53.
11. Rothstein JD, Kuncl RW. Neuroprotective strategies in a model of chronic glutamate-mediated motor neuron toxicity. J Neurochem 1995;65:643–651.
12. Hubert JP, Delumeau JC, Glowinski J, et al. Antagonism by riluzole of entry of calcium evoked by NMDA and veratridine in rat cultured granule cells: evidence for a dual mechanism of action. Br J Pharmacol 1994;113:261–267.
13. Herbert T, Drapeau P, Pradier L, et al. Block of the rat brain IIA sodium channel α subunit by the neuroprotective drug riluzole. Mol Pharmacol 1994;45:1055–1060.
14. Bensimon G, Lacomblez L, Meininger V, ALS/Riluzole Study Group. A controlled trial of riluzole in amyotrophic lateral sclerosis. N Engl J Med 1994;330:585–591.
15. Lacomblez L, Bensimon G, Leigh PN, ALS/Riluzole Study Group II. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. Lancet 1996;347:1425–31.
16. Tarone RE. Tests for trend in life table analysis. Biometrika 1975;62:679–682.
17. Horowitz S, Patwardhan R, Marcus E. Hepatotoxic reactions associated with carbamazepine therapy. Epilepsia 1988;29: 149–154.
18. Amato MP, Pracucci G, Ponziani G, Siracusa G, Fratiglioni L, Amaducci L. Long-term safety of azathioprine therapy in multiple sclerosis. Neurology 1993;43:831–833.

Discussion

DR. LUDWIG GUTMANN: What is the most controversial issue in evaluating riluzole clinical trial data: (1) lack of effect in secondary measures (51%); (2) reported difference in outcomes between geographical areas (20%); or (3) lack of quality-of-life data (28%)? The lack of effect of secondary measures is the greatest concern of the group.

Riluzole is approved as the first therapy for ALS. In which of the following circumstances would you prescribe riluzole: (1) in all patients with ALS (59%); (2) primarily in patients with rapid progression of ALS (4%); (3) recent diagnosis of ALS versus diagnosis made a few years ago (8%); or (4) only on the patient's request (29%)?

DR. MILLER: The data from the two studies[14,15] do not really guide us in terms of which patients are going to benefit from the use of riluzole. A large group of patients took the drug, and then at the end of the day there was a statistically significant difference between the placebo and riluzole-treated groups. In any neurologic disease, early intervention is more likely to be fruitful. There is experimental and clinical evidence to confirm that, with intervention early in many diseases, there is more likely to be a positive

benefit. However, it is difficult to draw that line and decide that a particular patient is not likely to benefit from the drug.

Lack of secondary measures is a very problematic issue. It is clear that no benefit could be demonstrated in either the manual muscle testing or in the functional scores. We have heard evidence that these are imprecise measures. It may also be that if these measures are used, more rigorous standardization across centers is needed. Another possibility is that this drug is working in ways that we do not fully understand.

DR. HANS NEVILLE (University of Colorado): It is possible that your placebo group behaved in a much worse fashion than placebo groups in other studies. Did you address that, and could you comment on the manuscript and its availability?

DR. MILLER: The manuscript was published a few months after this conference.[15] The issue about how well the placebo group did is a difficult one. The end point measure here is survival. There were differences in the survival of patients on placebo in different areas.

DR. MICHAEL STRONG (London, Ontario): A hazard function value of 1 implies that the probability of survival or death next day is no different from the preceding day; it is a time-to-failure model used by engineers, among others. In the data that you showed, your values for hazard functions were in the range of 0.001 for the placebo group, ranging up to about 0.015 to 0.02. That is a very small difference on a hazard function and, in fact, reveals that there is no significant difference in survivorship between the two. How do you reconcile that against the log rank data that weighs longer survival? Is your hazard function correct?

DR. MILLER: This effect is small. We are talking about a relatively modest difference in survival, but it is a difference that does achieve statistical significance by multiple measures. I am not going to quibble about the specifics of the ratio and the numbers.

DR. SALZMAN: Another way to look at the hazard ratio curve is the rate of death per unit of time. In a sense, it is looking at the slope of the Kaplan-Meier curve at, for example, 3-month intervals during the trial. Therefore, the numbers that you see are a function of a relatively flat slope, and the relatively small differences, or the difference between the hazard ratios, is really an index of the slope of the Kaplan-Meier curves. It is just another way of looking at the shape of the Kaplan-Meier curves and the difference between the curves over time.

DR. MILLER: Which is not very great.

DR. SALZMAN: Agreed.

DR. LEWIS P. ROWLAND: This may be a statistically significant difference. We are prolonging life, but by none of the measures of the rate of progression of the disease is there any effect. This is a contradiction, comparable to the spinal versus bulbar onset in the first study. Please comment.

Also, although the word "survival" is used all the time, there were patients who had tracheostomy and met end points. I have never seen the data that show how many patients had tracheostomies and how many died and whether there was a central difference in that. How was tracheostomy decided upon?

My last question concerns the placebo issue. Because there is no paper for us to deal with, we are constantly searching for who said what about what. At the FDA hearing I heard that, in France, the treated group did much better than the placebo group. In the rest of Europe, the placebo group and the treated group were equal, and in North America the patients did better if they were taking placebos. Please comment.

DR. MILLER: To answer your first question about why is there a lack of functional benefit even though there seems to be a statistically significant survival benefit: It is my opinion that the functional measures used as secondary measures—manual muscle testing and the Norris score—are insensitive and have to be standardized if they are to be used at all. This was not adequately addressed. There were no regular measurements of forced vital capacity, which would have been a very great addition to this study. The second question, about the number of tracheostomies and death: I showed a slide, "secondary survival analysis," that had death as an end point and excluded all patients with tracheostomy or intubation. It looked only at death. The placebo survival rate, when you look only at death, was 52%. The survival rate, when you look only at death, for 100 mg of riluzole, was 60%. The p values were 0.02 by the log rank and 0.02 by Wilcoxon.

DR. SALZMAN: I would like to add another piece of data. If we assume 1,000 patients were in the trial, roughly half of them were failures: death or tracheostomy. Of those roughly 500 failures, only about 10% were tracheostomies, and they were equally distributed among all four treatment groups. There was no inherent skewing of tracheostomies among the treatments. In fact, when you exclude tracheostomies as an end point, the difference between riluzole and placebo is even more clear and reaches lower p values.

DR. MILLER: As to the question about regional differences: a geographic post hoc subgroup analysis was not required. However, the FDA asked for a geographic analysis. First, the numbers in the North American study were small compared with the French/Belgian and other European studies. Also, the period that patients were on riluzole in North

America was shorter compared with Europe. In North America, the survival was better, particularly in placebo patients, than in French, Belgian, or other European patients. One possible reason is that there were several other trials ongoing in the United States at that time, and there was competition for patients from different trials. Therefore, some patients may have been enrolled at earlier stages of the disease than patients who had been cared for in a center for a long period as this may have occurred in some of the European centers. Care patterns may, in fact, be different, and survival might be different in North America compared with European countries. So if you look at that subset of North American patients, and consider other factors, a clear-cut benefit is not evident. But when the numbers at large are considered, the benefit is definite.

DR. HIROSHI MITSUMOTO: Actually, the FDA approved the medication, and it can be prescribed. I think that we are committed to continued research.