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WORKING GROUP ON ACUTE PURCHASING

The Use of Riluzole in the Treatment of Amyotrophic Lateral Sclerosis (Motor Neurone Disease)

August 1997

GUIDANCE NOTE FOR PURCHASERS 97/03
Series Editor: Nick Payne

Trent Development and Evaluation Committee

The purpose of the Trent Development and Evaluation Committee is to help health authority and other purchasers within the Trent Region by commenting on expert reports which evaluate changes in health service provision. The Committee is comprised of members appointed on the basis of their individual knowledge and expertise, and includes non-clinically qualified scientists and lay members. It is chaired by Professor Sir David Hull.

The committee recommends, on the basis of appropriate evidence, priorities for:

- the direct development of innovative services on a pilot basis;
- service developments to be secured by health authorities.

The statement that follows was produced by the Development and Evaluation Committee at its meeting on 22 July 1997 at which this Guidance Note for Purchasers (in a draft form) was considered.

THE USE OF RILUZOLE IN THE TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS (MOTOR NEURONE DISEASE)

AUTHORS: Chilcott J, Golightly P, Jefferson D, McCabe C and Walters S. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield, 1997. (Guidance Note for Purchasers: 97/03)

EXPERT ADVISOR TO TRENT DEC: Mr Chilcott, Senior Analyst from ScHARR.

SUMMARY:
Amyotrophic lateral sclerosis (ALS), a form of motor neurone disease, is a progressive and fatal neurodegenerative disorder with a very poor prognosis; from the onset of symptoms, five year survival is 5-15%, with a median survival time of about three years. Prior to the introduction of riluzole, only symptomatic and supportive care has been available.

Two randomised controlled trials show that treatment with riluzole for up to 18 months significantly increases survival in ALS. Riluzole retards disease progression to a limited extent, but does not appear to arrest the disease and, on current evidence, it provides no other subjective or objective improvements. Quality of life studies have not been undertaken.

However, the short duration of the two studies and the adjustment for prognostic factors means that there is a high level of uncertainty in the benefits achieved from the use of riluzole. The cost per life year gained over 18 months of treatment obtained from a direct analysis of the trial data as published, is approximately £50,000, with a lower estimate of £22,000 and worst case of no benefit observed. When results are adjusted for prognostic factors and modelled over 10 years, the mid-range estimate is £27,600 per life year gained.

The cost of treatment is about £3,700 per patient year. The total annual cost for a typical district of 500,000 population providing riluzole therapy to all ALS patients is approximately £99,000. This, however, represents a maximum as not all patients would be eligible for, or would request, treatment.

DECISION: The Committee felt unable to support the funding of Riluzole on either an unlimited or limited basis because of the uncertainties in the interpretation and analysis of trial evidence on survival, the lack of quality of life information, the limited benefit that is actually claimed, and the high cost-effectiveness ratio even when derived from adjusted trial data.

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Conflict of Interest None of the authors of this document has any financial interests in the drug or product being evaluated here.

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We should also like to acknowledge the European Agency for the Evaluation of Medicinal Products for allowing us to reproduce the 'Opinion of the CPMP on the granting of a marketing authorisation for Rilutek'.

ABOUT THE TRENT INSTITUTE FOR HEALTH SERVICES RESEARCH

The Trent Institute for Health Services Research is a collaborative venture between the Universities of Leicester, Nottingham and Sheffield with support from NHS Executive Trent.

The Institute:

- provides advice and support to NHS staff on undertaking Health Services Research (HSR);
- provides a consultancy service to NHS bodies on service problems;
- provides training in HSR for career researchers and for health service professionals;
- provides educational support to NHS staff in the application of the results of research;
- disseminates the results of research to influence the provision of health care.

The Directors of the Institute are: Professor R L Akehurst (Sheffield);
Professor C E D Chilvers (Nottingham); and
Professor M Clarke (Leicester).

Professor Akehurst currently undertakes the role of Institute Co-ordinator.

A Core Unit, which provides central administrative and co-ordinating services, is located in Regent Court within the University of Sheffield in conjunction with the School of Health and Related Research (ScHARR).

FOREWORD

A network exists in the Trent Region where purchasers can share research knowledge about the effectiveness and cost-effectiveness of acute service interventions and determine collectively their purchasing policy.

ScHARR, which houses the Sheffield Unit of the Trent Institute for Health Services Research, facilitates a Working Group on Acute Purchasing. A list of interventions for consideration is recommended by the purchasing authorities in Trent and approved by the Purchasing Authorities Chief Executives (PACE) and the Trent Development and Evaluation Committee (DEC). A public health consultant from a purchasing authority leads on each topic and is assisted by a support team from ScHARR, led by Dr Nick Payne, Senior Lecturer in Public Health Medicine, which provides help including literature searching, health economics and modelling. A seminar is then led by the consultant on the particular intervention where purchasers and provider clinicians consider research evidence and agree provisional recommendations on purchasing policy. The guidance emanating from the seminars is reflected in this series of Guidance Notes which have been ratified by the Trent DEC which is chaired by Professor Sir David Hull.

The Trent Institute's Working Group on Acute Purchasing is part of a wider collaboration working with three units in other regions (The Wessex Institute for Health Research and Development, The Scottish Health Purchasing Information Centre (SHPIC) and The Birmingham University Institute for Public and Environmental Health) to share this work on reviewing the effectiveness and cost-effectiveness of clinical interventions. This group, InterDEC, will share this work, avoid duplication and improve the peer reviewing and quality control of these reports.

Professor R L Akehurst,
Chairman, Trent Working Group on Acute Purchasing.

CONTENTS **Page**

LIST OF TABLES AND FIGURES **Page**

EXECUTIVE SUMMARY

- Amyotrophic lateral sclerosis (ALS), a form of motor neurone disease, is a progressive and fatal neurodegenerative disorder with a very poor prognosis; from onset of symptoms five year survival is 5-15%, with a median survival time of about three years. Prior to the introduction of riluzole, only symptomatic and supportive care has been available.

- Riluzole ('Rilutek', Rhone-Poulenc Rorer) is a new drug licensed throughout the European Union and in the United States for use to extend life or the time to mechanical ventilation in patients with ALS. It was marketed in the UK in August 1996.

- Two randomised controlled trials report that treatment with riluzole for up to 18 months significantly increases survival in ALS. In the first study, 58% of patients on placebo and 74% on riluzole were alive at 12 months. In a second, larger, study, 50% of patients on placebo were alive at 18 months compared with 57% on riluzole 100 mg daily. Simple compararison of the survival in these trial groups shows no significant difference, although, after adjustment for prognostic factors, a modest improvement in survival is demonstrated.

- The European Agency for the Evaluation of Medicinal Products (EMEA) in its conclusions in consideration of a marketing authorisation for Rilutek, (see Appendix A), said 'treatment with riluzole does not demonstrate a positive effect on functional symptoms of the disease whilst the magnitude of the effect on survival is modest. There are therefore remaining uncertainties on the product in the management of Amyotrophic Lateral Sclerosis'.

- The lack of information regarding long-term survival benefits, caused by the short duration of the two studies, means that there is a level of uncertainty in the likely benefits achieved from the use of riluzole. An analysis of these uncertainties is presented in this report. Furthermore, it should be noted that there is some debate about the process of adjusting for prognostic factors used in the trial analysis.

- The cost per life year gained over 18 months of treatment obtained from an unadjusted analysis of the trial data as published, is approximately £50,000, with a lower estimate of £22,000 and worst case of no benefit observed. When results are adjusted for prognostic

factors and modelled over a 10 year time horizon, under a range of different assumptions, the cost per life year gained is estimated to range between £14,800 and £41,000. The mid range estimate is £27,600 per life year gained.

- The unadjusted trial data imply that it would be necessary to treat 11 patients for up to 18 months to obtain one additional life year, that is the number needed to treat (NNT). Over the 10 year horizon the adjusted NNT ranges from two to seven. The central estimate is four.

- Therefore, riluzole appears, at best, to offer modest clinical benefit in patients with ALS; it retards disease progression to a limited extent, but does not appear to arrest the disease and, on current evidence, it provides no other subjective or objective improvements. Quality of life studies have not been undertaken. Nevertheless, riluzole is an important step forward in the management of ALS.

- The cost of treatment is about £3,700 per patient year.

- The total annual cost for a typical district of 500,000 population of providing riluzole therapy to all ALS patients is approximately £99,000. This, however, represents a maximum as not all patients would be eligible for, or would request, treatment.

- On current evidence, riluzole treatment should be limited to those patients most likely to benefit clinically, the selection of whom should be against agreed clinical criteria. The inclusion criteria of the clinical trials provide a baseline set of clinical criteria. However, further work should be undertaken to identify sub-groups of patients who would benefit significantly from treatment, either on the basis of a further analysis of the clinical trial data, or from other on-going primary research. Unpublished trial evidence indicates that no benefit is obtained from riluzole treatment in the population excluded from the trial under the exclusion criteria.

- The uncertainty in long-term survival benefits means that mandatory monitoring of mortality and morbidity should be associated with treatment.
- It is expected that treatment should normally be initiated on the advice of a consultant neurologist. However, riluzole appears to be relatively safe, which makes the transfer of subsequent prescribing to GPs viable, depending on local policies and arrangements.

1. INTRODUCTION

1.1 Motor Neurone Disease: Background to Disease

Motor neurone disease (MND) is a progressive devastating neurological disorder involving motor neurones in the brain and spinal cord.[1] About 5% of cases are familial. Several possible causes have been suggested including toxic activation of motor neurone glutamate receptors, excessive formation of free radicals and possible auto-immune mechanisms. There is no conclusive evidence to implicate any of these factors but, at present, glutamate related mechanisms appear to offer the most potential for research and treatment. MND has classically been divided into three forms - progressive muscular atrophy, amyotrophic lateral sclerosis (ALS) and progressive bulbar palsy. ALS and progressive bulbar palsy are usually manifestations of the same illness but progressive muscular atrophy is a heterogeneous group, only a proportion of which is part of the ALS syndrome.

1.2 Prognosis and Mortality

ALS presents with a mixture of spasticity and muscle wasting. It can begin in the bulbar or spinal muscles, although both eventually become involved as the disease progresses. The bulbar form causes dysarthria and dysphagia resulting in loss of communication and nutritional problems. The spinal form presents with wasting and spasticity of one or more limbs, progressing with time. Respiratory muscles eventually become involved and a minority of patients present with respiratory failure. Intellectual deterioration is rare and involvement of ocular muscles and the bladder and bowel are unusual.

Following presentation, the symptoms of ALS progress relentlessly. Conventional treatment is symptomatic and supportive and death commonly results from respiratory complications. Some patients are offered ventilatory support.

The median survival from first symptoms in those with bulbar onset is about two years, with only 5% surviving five years. The median survival for those with spinal onset is about 2.5 years, with nearly 15% surviving five years.

1.3 Prevalence and Incidence

The prevalence of ALS is about 4-6 per 100,000 population, with an incidence of 1-1.5 per 100,000 per year.[2] Males are affected more often than females and incidence increases with age; onset of ALS usually occurs after 50 years of age.

Based on current estimates of prevalence, there may be up to 280 people with ALS in the Trent region. In a typical district of 500,000 people, between five and eight new cases of MND would be expected per year. At any one time there would be between 20 and 30 patients with MND.

1.4 Riluzole and Motor Neurone Disease

Riluzole ('Rilutek', Rhone-Poulenc Rorer) is a new drug which is believed to act by blocking the toxic effects of excessive glutamate on nerve cells. In 1994, Bensimon et al. published a trial of a new pharmaceutical treatment for MND, riluzole, which indicated that riluzole produced mortality and morbidity benefits.[3] It has received marketing authorisation throughout the European Union through the centralised European Agency for the Evaluation of Medicinal Product (EMEA) / Committee for Proprietary Medicinal Products (CPMP) procedure, and in North America. It was launched in the UK in August 1996, and is indicated for use to extend life, or time to mechanical ventilation, in patients with ALS.

2. USE OF RILUZOLE IN THE TREATMENT OF MOTOR NEURONE DISEASE : SUMMARY OF EVIDENCE OF EFFECTIVENESS

2.1 Summary of Evidence of Effectiveness of Riluzole

Two major studies into the clinical effectiveness of riluzole in the treatment of MND have been published.[3,4] These trials were undertaken by the same research group led by Lacomblez and Bensimon and both studies constituted prospective, randomised and double-blind placebo trials. Details of these trials are summarised in Table 1. Both had similar entry criteria, including clinically probable or definite ALS of no greater than five years' duration; forced vital capacity of at least 60% of that predicted for patients' age and height; and exclusion of patients with tracheostomy, renal dysfunction, and life threatening or incapacitating disease. The primary outcome measure was defined as tracheostomy-free survival during the double-blind period; end-points were death from any cause, tracheostomy, and intubation with artificial ventilation leading to tracheostomy.

The first study randomised 155 patients into two groups, either bulbar-onset (n=32) or limb-onset (n=123), which received riluzole 100 mg daily or placebo.[3] Overall, 74% of riluzole patients were alive at 12 months, compared with 58% on placebo. In the bulbar-onset group 73% were alive with riluzole compared with 35% on placebo and, in the limb-onset group, this figure was 74% compared with 64%.

A second, larger, study looked at different doses of riluzole in 959 patients.[4] Of 236 patients taking 100 mg riluzole daily, 57% were alive after 18 months, compared with 50% of 242 taking placebo. Eighteen-month survival for patients taking 200 mg or 50 mg was 58% and 55% respectively. Statistical analysis of the trial data, using a Cox Proportional Hazards Model to adjust for prognostic factors in the trial population, showed that 100 mg riluzole per day reduced the instantaneous hazard ratio at the 18 month timepoint by 35%, all other risk factors being equal (relative risk = 0.65, 95% CI = 0.5-0.85, p=0.002). This cannot, however, be interpreted as a 35% reduction in 18 month mortality - any reduction that does occur through treatment would certainly be less than this.

Bensimon et al. described a significant improvement in one year survival for bulbar-onset disease, with a non-significant effect on limb-onset ALS.[3] The survival effect in the bulbar-onset group was large enough such that the difference for those patients was seen in the entire trial population. Lacomblez et al. randomised patients by centre and by disease site-

onset as in the smaller study. They stated that outcomes were similar in patients with bulbar or limb-onset, although these data were not included in the results. Overall, a significant improvement in survival was shown.

Both studies also looked at secondary outcomes:

- Muscle strength assessed for 22 muscle groups with the patient in the sitting position, according to the Medical Research Council five-grade scale.
- Functional status.
- Respiratory function (vital capacity).
- Patients' subjective assessment of fasciculations, cramps, stiffness, and tiredness.
- Clinicians' global impression.

No quality of life measurements were included. Overall, neither study showed significant improvement in secondary outcomes. However, the smaller study demonstrated significant improvement in muscle-testing scores (33% reduction in the rate of deterioration of muscle function). The second study showed no significant change in any secondary outcome measures.

The absence of data showing beneficial effects of riluzole on quality of life or functionality is of concern. However, objective methods of evaluating motor function in ALS are relatively insensitive. Patients with ALS continue to deteriorate during treatment; the drug retards, but does not arrest, disease progression. It is perhaps unsurprising, therefore, that differences in functionality could not be demonstrated in the clinical trials. Further work in this area is under way.

Table 1: Summary of Clinical Trials

TRIAL	BENSIMON ET AL[3]			LACOMBLEZ ET AL[4]	
DESIGN	Prospective, randomised, double-blind placebo controlled			Prospective, randomised, double-blind, placebo controlled	
PATIENT NUMBERS	155 (32 bulbar, 123 spinal)			959 (295 bulbar, 664 spinal)	
INCLUSION CRITERIA	age 20-75 probable/definite ALS of no longer than 5 years, >60% predicted FVC*			age 18-75 probable/definite ALS of no longer than 5 years, >60% predicted FVC*	
EXCLUSION CRITERIA	Tracheostomy, renal dysfunction, other life-threatening or incapacitating disease			Tracheostomy, renal dysfunction, other life-threatening or incapacitating disease	
PRIMARY END -POINT	Death or tracheostomy at 12 months**			Death or tracheostomy at 18 months**	
STUDY PERIOD	365 days			442-548 days	
DAILY DOSE	100 mg			50, 100, 200 mg	
OVERALL SURVIVAL	**12 months** **Bulbar** **Spinal** **All**	**Riluzole** 11/15(73%) [p=0.014] 46/62(74%) [p=0.17] 57/77(74%) [p=0.014]	**Placebo** 6/17(35%) 9/61(64%) 45/78(58%)	**Dose** 50mg 100mg 200mg All Placebo	**Survival - 18 months** 131/237 (55%) 134/236 (57%) 141/244 (58%) 406/717 (57%) 122/242 (50%)
INSTANTANEOUS RELATIVE RISK AT 12 MONTHS TIME-POINT OF TREATMENT OVER PLACEBO	**Dose** 100mg 0.43 (0.24 - 0.77) [p=0.005]			**Dose** **Unadjusted analysis - Table 3** 50mg 0.85 (0.66 - 1.11) [p=0.25] 100mg 0.79 (0.6 - 1.02) [p=0.076] 200mg 0.79 (0.61 - 1.03) [p=0.075] All 0.81 (0.66 - 0.99) [p=0.048] **Adjusted analysis - Table 4** 50mg 0.76 (0.59 - 0.99) [p=0.04] 100mg 0.65 (0.50 - 0.85) [p=0.002] 200mg 0.61 (0.47 - 0.80) [p=0.0004]	
WITHDRAWAL DUE TO ADVERSE EVENTS	27 on riluzole 17 on placebo			50 on placebo 48 riluzole 50 mg 54 riluzole 100 mg 53 riluzole 200 mg	

* Forced Vital Capacity

** Secondary end-points included limb and bulbar function, respiratory function, patients' subjective evaluations of cramps, fasciculations, stiffness, tiredness, clinicians' global impression.

2.2 Adverse Effects and Monitoring

Adverse events were frequent in all study groups, for example, in the larger study 103/236 (44%) patients treated with riluzole 100 mg reported respiratory system problems, compared with 115/242 (48%) patients on placebo. Many of the events are likely to be a direct result of ALS. Overall, riluzole was well tolerated in the clinical trials. However, a small, but important, number of patients had adverse events which could be directly attributable to treatment with riluzole. In particular, 85/717 (12%) had liver function test (LFT) disturbances, compared with 9/242 (4%) on placebo. Neutropenia was reported in three cases from phase III clinical trials. Clinical experience suggests that about 5% of patients withdraw from treatment because of adverse effects directly attributable to riluzole. The most common adverse reactions reported are asthenia, nausea and anorexia, which occur in 4-5% of patients, and abnormal LFTs. Nausea and anorexia may respond to anti-emetics.

Therefore, riluzole should be prescribed with care in patients with a history of abnormal liver function. Serum transaminases should be measured before starting treatment, monthly during the first three months, every three months in the remainder of the first year, and periodically thereafter. Transaminases should be monitored more frequently in patients who develop disturbances in liver function. Treatment should be stopped in patients whose ALT rises to five times the upper limit of normal. On present evidence, resumption of treatment is not recommended. In view of the reported cases of neutropenia, a full blood count should be performed regularly.

2.3 Conclusion on Direction of Evidence and its Quality

Riluzole treatment for up to 18 months has been shown to increase survival significantly in ALS. Although it retards disease progression, riluzole does not appear to arrest the disease and, on current evidence, it provides no other objective or subjective improvement. Nevertheless, riluzole is an important step forward in the management of people with ALS, which has hitherto been supportive and palliative.

3. COST AND BENEFIT IMPLICATIONS OF ADOPTING INTERVENTION

3.1 Analytical Overview

Riluzole is the first treatment for MND to have shown mortality and morbidity benefits. These benefits have been identified in two published studies both undertaken by the same research group. As in all cases where there is such limited trial evidence there is significant uncertainty concerning the effectiveness of the treatment and, therefore, also in the related economic analysis. The two main sources of uncertainty in the economic analysis of riluzole are:

- interpretation of the published RCT results for the 18 month period covered by the trial, specifically in terms of assessing the implications of prognostic factors on survival benefits;
- long-term survival profiles beyond the 18 month period of the trial.

The analysis presented here is based on the Lacomblez, Bensimon trial,[4] the second and larger of the two published trials. The analysis focuses on the 100mg riluzole treatment group. The 50mg and 200mg treatment groups included in the RCT are not analysed here as these regimens are not licensed for use in the UK.

The published statistical analysis of the trial[4] includes adjustment for demographic and prognostic factors in the trial population. This adjustment has a marked effect on the benefits seen in the treatment group. The use of the hazard ratio, obtained from the Cox Proportional Hazards model, for demonstrating treatment effects means that the underlying baseline hazard, and thus baseline survival, are not evaluated. Further, insufficient information is given to quantify the baseline hazard and hence produce a complete survival analysis. Clearly, to assess the benefits in terms of survival, and hence life years gained, some measure of baseline survival is required. In this analysis a parametric baseline hazard function from the Weibull distribution has been assumed. This assumption cannot be tested without access to the raw trial data, thus there is a level of uncertainty in the adjusted outcomes. To address this issue an analysis based on the unadjusted trial results is first presented; this is followed by an analysis adjusted for prognostic factors.

The trial was stopped after 18 months, thus, there are no data available to evaluate the long-term effects of riluzole treatment. To address this issue a range of assumptions is considered for the long-term survival patterns beyond the 18 month trial period.

The survival estimates and total costs are presented for a typical district population of 500,000 under a range of prevalence and incidence rates.

3.2 Cost-benefit Analysis Based on Trial Data with no Adjustment for Differences Between Prognostic Characteristics of Treatment Groups

3.2.1 Unadjusted Survival Analysis for 18 Month Trial Period

Table 2 and Figure 1 below give trial data and Kaplan-Meier tracheostomy-free survival estimates derived used an actuarial methodology.

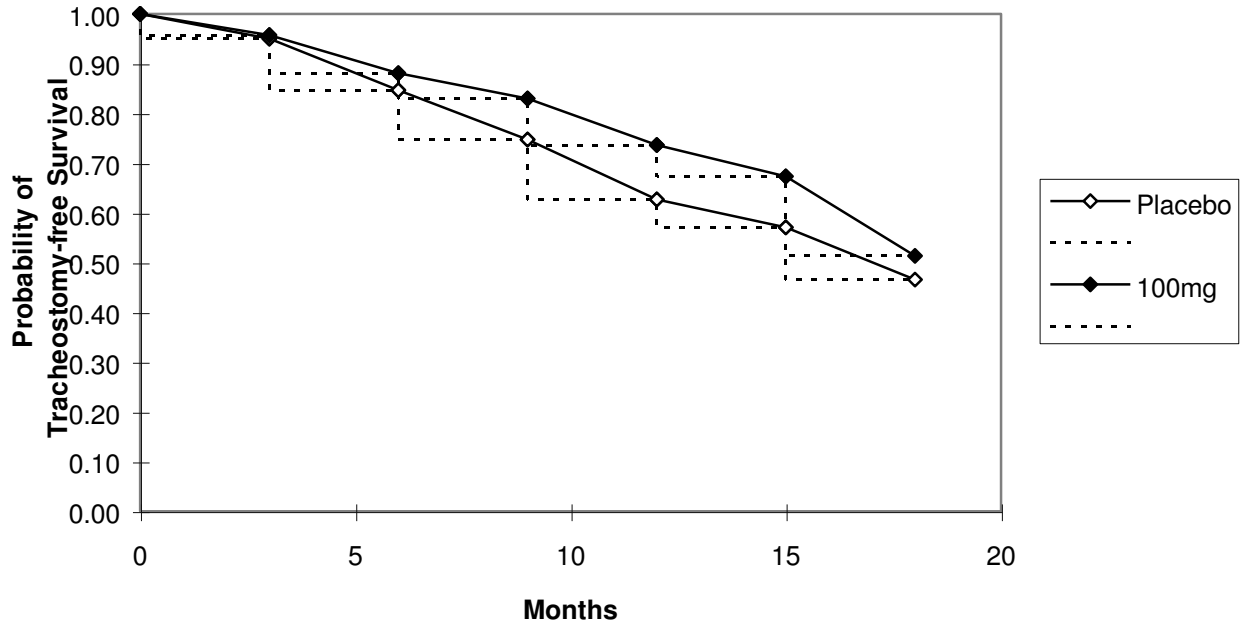
Table 2: Kaplan-Meier Survival Estimates for 18 Month Trial Period

MONTHS	AT RISK (PERIOD START)		DEATH OR TRACH. (Cum.)		CENSORED (Cum.)		SURVIVAL PROBABILITY	
	PLACEBO	100MG	PLACEBO	100MG	PLACEBO	100MG	PLACEBO	100MG
0 - 3	242	236	12	10	0	1	95%	96%
3 - 6	230	225	37	28	1	1	85%	88%
6 - 9	204	207	61	40	1	1	75%	83%
9 - 12	180	195	90	62	1	1	63%	74%
12 - 15	151	173	103	76	12	18	57%	67%
15 - 18	127	142	120	102	81	83	47%	51%

At 12 months the probability of tracheostomy-free survival for the 100mg treatment group is 74% compared to 63% for the placebo group; at 18 months the survival probabilities are 51% and 47% respectively.

Figure 1 shows the Kaplan-Meier step functions (---) obtained from the actuarial analysis of the published three monthly interval data, together with simple straight line interpolations between the interval end-points. The life years gained are calculated from the area between the interpolated placebo and 100mg survival plots. The average 100mg treatment cost per patient over 18 months is calculated from the area under the 100mg treatment survival curve (adjusted from months to years) multiplied by the cost per year of treatment.

Figure 1: Kaplan-Meier Tracheostomy-Free Survival Plots



Thus, over the 18 month trial period the 100mg treatment results in approximately 0.1 life years gained per patient, or just over 1 life month.

The cost of riluzole is £286 per pack of 56 50mg tablets.[5] The cost of drugs for one year of treatment on the 100mg per day dosage is approximately £3,720. The expected cost of drugs up to tracheostomy or death over an 18 month period is approximately £4,500. Therefore, if no adjustment is made for prognostic factors in the different patient groups, **the cost per life year gained over the 18 month period is approximately £50,000**.

A range of estimates for the cost-effectiveness can be derived from the 95% confidence intervals for the Kaplan-Meier survival estimates of the treatment group and placebo group. It should be noted that, without adjusting for covariance between the two groups, this gives an overestimate of the variance of the benefit in terms of life years gained. However, with this proviso, it is important to note that the 95% confidence interval for life years gained includes no benefit. This is the corollary to the reported 95% confidence interval for the hazard ratio which includes a hazard ratio of 1, see Table 3 in the Lacomblez article.[4] At the other end of the scale the 95% confidence limit results in a cost per life year gained of approximately £22,000.

The life years gained imply that it would be **necessary to treat 11 patients for up to 18 months to obtain one additional life year**, that is the number needed to treat (NNT). The lower 95% confidence limit for the NNT is five, the higher limit is infinite where no benefit is obtained from treatment.

3.2.2 Unadjusted Long-term Survival Analysis

Another major area of uncertainty in the analysis is the lack of trial data beyond 18 months. A range of possible assumptions regarding the survival profiles over 18 months have been investigated in order to calculate the implications for the cost-effectiveness of riluzole. The analysis presented below is based on the actual trial estimates for the period 0 to 18 months together with three different assumptions regarding survival profiles beyond 18 months.

Assumptions concerning the long-term survival for MND patients:

A0 *No treatment or placebo group:*
It is assumed that the hazard or risk of death is constant and independent of time since inclusion in the trial; the rate used is that indicated at the 18 month point in the trial for the placebo group.

A1 *100 mg treatment group - worst case:*
It is assumed that there is a sudden increase in death rate between 18 and 24 months resulting in a return to placebo group survival levels at two years. Assuming that there are no toxic effects from long-term riluzole treatment, this is an absolute worst case assumption.

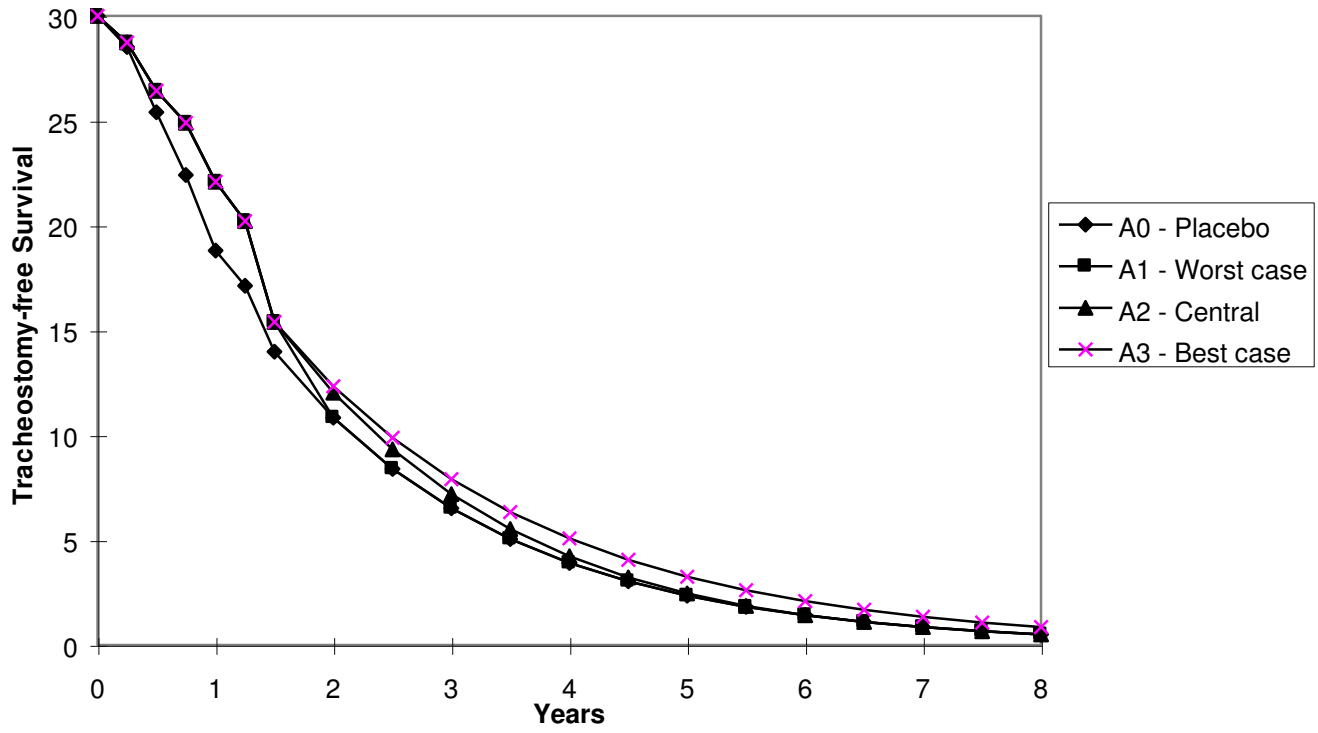
A2 *100 mg treatment group - mid-case:*
It is assumed that the hazard rate increases with time since inclusion in the trial after 18 months. (Note that this assumption implies that the hazard rate or risk of death after 18 months is greater in the treatment group than in the placebo group).

A3 *100 mg treatment group - best case:*

It is assumed that the hazard rate is constant and independent of time since inclusion in the trial (that is a constant hazard rate), the rate used is that indicated at the 18 month point in the trial for the 100mg treatment group.

The survival profiles implied by the above assumptions are given in Figure 2.

Figure 2: Long-term Survival for Cohort of 30 Patients



The placebo treatment, assumption A0, is assumed to be associated with a constant age specific death rate. This assumption is supported by the proportional hazards model suggested by Haverkemp et al.[6] and the exponential survival pattern suggested by Norris et al.[7] Assumption A1, the worst case estimate, would require a sudden sharp increase in the death rate over the 18-24 month period. This assumption represents the worst case scenario, that the benefit from riluzole treatment is short-lived, and only suspends the progression of the disease during the first 18 month period; this would imply a very high death rate in the 18-24 month period. Assumption A2 represents a mid-case estimate where the hazard or risk of death in the treatment group increases after the 18 month period. This implies that benefits from riluzole treatment cease after 18 months and that survival deteriorates back to placebo levels after just over three years. Assumption A3 implies that

the constant age-specific rate of death indicated at the 18 month period is maintained throughout the rest of the natural progression of the disease. This is not strictly a best case since it assumes that there are no long-term benefits arising from the cumulative effect of drug therapy and also that no long-term delay in disease progression results from therapy. Thus, it may be argued that this is a conservative best case assumption.

The following tables give the resultant expected survival and costs profiled over a 10 year horizon for an original cohort of 30 patients under placebo treatment, A0, and under the 100mg treatment with the three long-term survival assumptions A1, A2 and A3.

Table 3: Unadjusted Survival within the Cohort

YEAR	PLACEBO	A1	A2	A3
0	30.0	30.0	30.0	30.0
1.5	14.0	15.4	15.4	15.4
3	6.5	6.5	7.2	7.9
5	2.4	2.4	2.5	3.3
10	0.2	0.2	0.2	0.4

Table 4: Unadjusted Life Years Gained and Total Cost

YEAR	CUMULATIVE LIFE YEARS GAINED			TOTAL COST (Cum.)		
	A1	A2	A3	A1	A2	A3
1.5	2.7	2.7	2.7	£134,800	£134,800	£134,800
3	3.1	4.3	4.9	£191,000	£195,500	£197,800
5	3.1	5.0	7.2	£221,500	£228,600	£237,000
10	3.1	5.0	9.5	£237,400	£244,700	£261,400

Table 5: Unadjusted Cost per Life Year Gained

YEAR	A1	A2	A3
1.5	£50,000	£50,000	£50,000
3	£62,500	£45,700	£40,400
5	£72,500	£46,000	£32,800
10	**£77,700**	**£48,900**	**£27,500**

Table 6: Unadjusted Number Needed to Treat

YEAR	A1	A2	A3
1.5	11.1	11.1	11.1
3	9.8	7.0	6.1
5	9.8	6.0	4.2
10	**9.8**	**6.0**	**3.2**

Under the worst case scenario, assumption A1, no life years benefit is obtained after eighteen months, however, the cost of riluzole treatment still accrues over the 10 year time horizon, leading to a very high cost per life year gained. Under the mid-range assumption A2, even though no positive benefit is obtained from riluzole after 18 months, the slower return to placebo survival levels means that the cost per life year gained is stable at around £50,000. Assumption A3 assumes that the benefits from riluzole are maintained and result in a cost per life year gained over the 10 year period of £27,500.

3.3 Cost-benefit Analysis Based on Trial Results Adjusted for Differences between Prognostic Characteristics of Treatment Groups

3.3.1 Adjusted Survival Analysis for 18 Month Trial Period

The published trial analysis identifies 10 demographic and clinical baseline variables as independent prognostic factors in disease progression. The placebo and 100mg treatment groups were not randomised over these 10 factors and hence adjustment is necessary to account for the different population characteristics in each group.

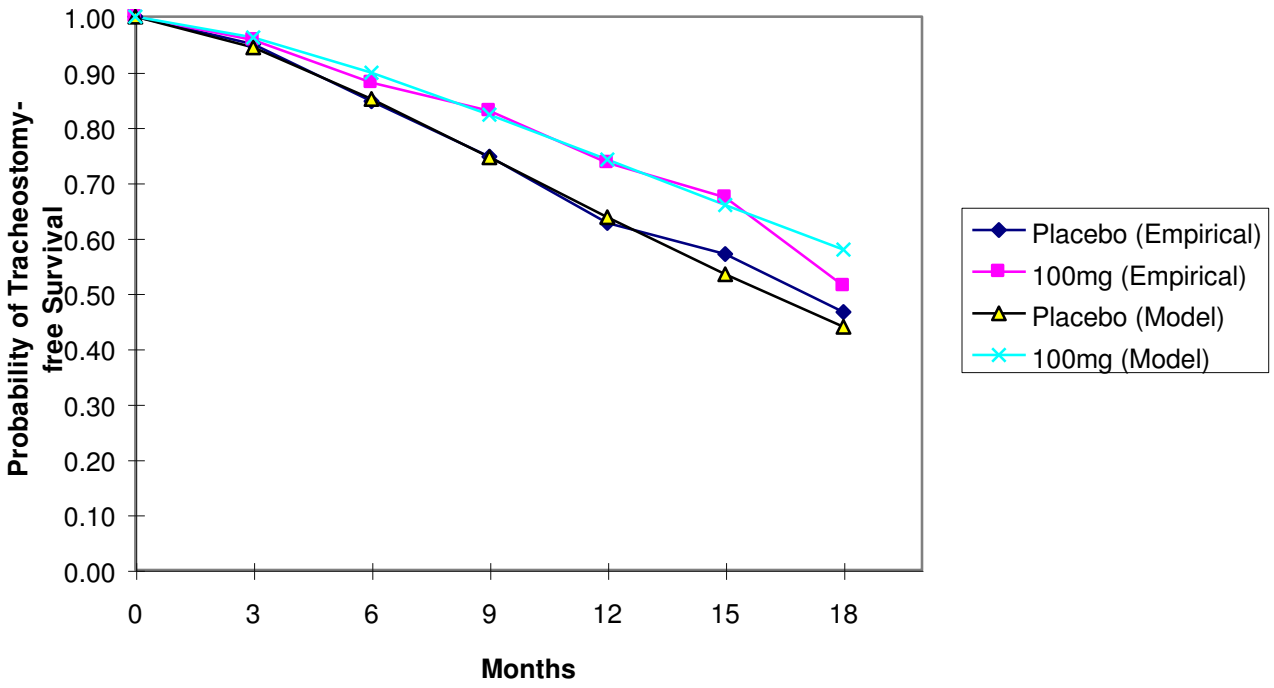
A Cox Proportional Hazards Model is used to undertake this adjustment. A review of this model and the implementation described in the published paper is included in Appendix B. To summarise, the hazard at any point in time for an individual is defined as the risk of dying in a very short time interval given that the individual has survived to the start of that interval. The basis of the Cox Proportional Hazards model is that the hazard or risk at any point in time is assumed to be proportional to each of the prognostic factors. The Cox model is a semi-parametric model and makes no assumption about the underlying survival characteristics of the population. Thus, whilst the model allows comparisons to be made between treatment groups no absolute measure of survival is obtained.

In order to obtain an absolute estimate of the survival adjusted for prognostic factors from the information provided in the published paper, it is necessary to make an assumption regarding the form of the baseline hazard:

A4 In order to estimate the survival in the placebo and treatment groups from the hazard information presented in the published paper, the analysis presented here assumes a Weibull baseline hazard function.

Figure 3 shows the empirical survival plots, against a Cox Proportional Hazards Model with baseline hazard function from the Weibull distribution. The model is based on the treatment group profiles as detailed in Table 1 of the published article and the prognostic scores given in Table 4 of the article. The parameters of the baseline function are estimated by minimising the least squares difference between the model estimates at three monthly intervals and the interval estimates from the actuarial analysis described in Section 3.2.1.

Figure 3: Empirical Survival Plots and Best Fitted Survival from Cox Proportional Hazards Model with Weibull Baseline Hazard Function



The survival for the placebo and 100mg treatment groups is then adjusted to the estimated survival for a population with the same characteristics as the total trial population.

It should be emphasised that these adjustments are made to account for differences between treatment groups within the trial. Furthermore, if the ALS population in a district has markedly different characteristics from the trial population then further adjustments may be appropriate in assessing the implications of riluzole use in that population.

The life years gained and the drug treatment costs are calculated as in Section 3.2.1. The expected cost per life year gained over the 18 month period after adjustment for prognostic factors falls to £39,000. It would be necessary to treat approximately nine patients for up to 18 months in order to achieve one life year benefit.

3.3.2 Long-Term Survival Analysis Adjusted for Prognostic Factors

A similar set of assumptions regarding long-term survival patterns are explored for the adjusted analysis. Figure 4 presents the survival profiles under the three assumptions considered.

Figure 4: Adjusted Long-term Survival for Cohort of 30 Patients

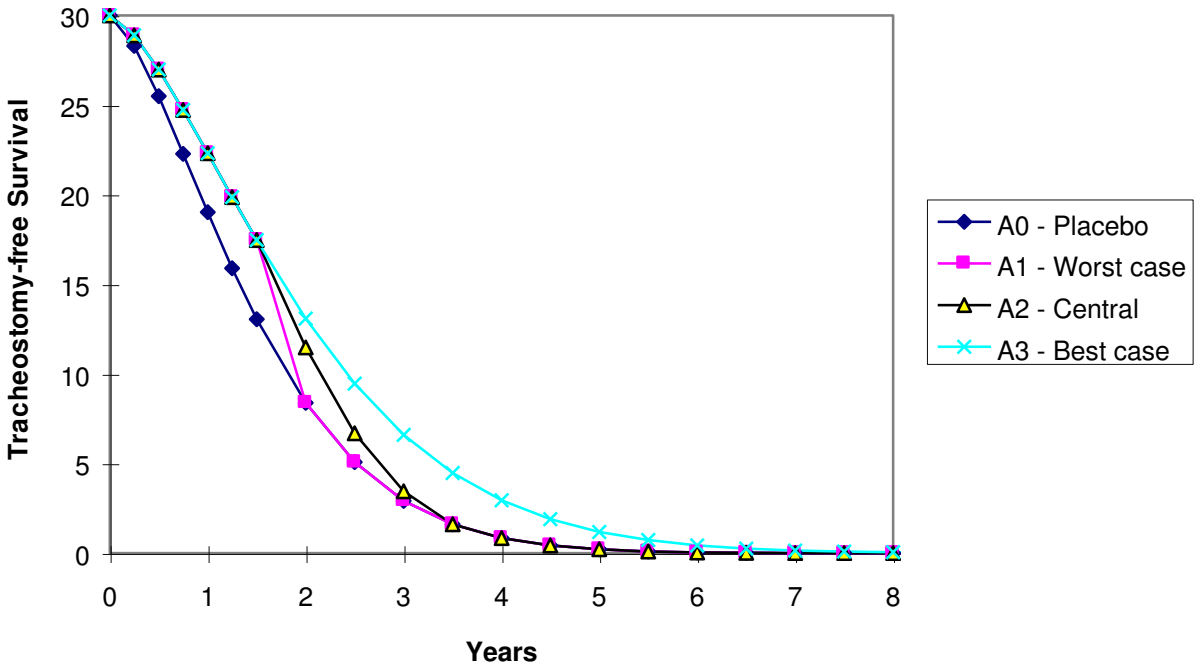


Table 7: Adjusted Survival in the Cohort

YEAR	PLACEBO	A1	A2	A3
0	30.0	30.0	30.0	30.0
1.5	13.1	17.5	17.5	17.5
3	2.9	2.9	3.4	6.6
5	0.2	0.2	0.2	1.2
10	0.0	0.0	0.0	0.0

Table 8: Adjusted Life Years Gained and Total Costs

YEAR	A1	A2	A3	A1	A2	A3
1.5	3.5	3.5	3.5	£136,200	£136,200	£136,200
3	4.6	7.1	10.1	£180,100	£189,400	£200,500
5	4.6	7.2	14.4	£188,400	£198,100	£225,000
10	4.6	7.2	15.5	£188,900	£198,600	£229,300

Table 9: Adjusted Cost per Life Year Gained

YEAR	A1	A2	A3
1.5	£39,000	£39,000	£39,000
3	£39,200	£26,800	£19,900
5	£41,000	£27,500	£15,600
10	**£41,100**	**£27,600**	**£14,800**

Table 10: Adjusted Number Needed to Treat

YEAR	A1	A2	A3
1.5	8.6	8.6	8.6
3	6.5	4.2	3.0
5	6.5	4.2	2.1
10	**6.5**	**4.2**	**1.9**

The large decrease in cost per life year gained and in NNT between 18 months and the 10 year time horizon emphasises the importance of long-term survival patterns in the cost-effectiveness of riluzole. This highlights the need to undertake long-term monitoring of patient survival if riluzole treatment is undertaken.

The estimates of cost per life year gained, under the assumptions presented in this report, range between £14,800 under the best case assumption of maintained benefits from riluzole to £41,000 under the worst case assumption. The mid-range estimate is £27,600 per life year gained.

The estimate of the adjusted number NNN is four and ranges from two to seven.

Using the Treasury discount rate of 6% to discount both costs and benefits the discounted cost per life year gained figure is £28,200. This increase reflects the fact that the majority of the costs are incurred in the early years whilst the majority of the life years benefits are achieved later in treatment.

Table 11 below gives the total costs per annum associated with 100mg riluzole treatment for a district population of 500,000. These costs assume that the entire MND prevalence population uses riluzole treatment irrespective of the time since onset of disease, age or contra-indicating factors. In addition, a proportion of patients may not take up treatment due to the lack of proven functional or quality of life benefit. Therefore, these figures are likely to be overestimates; a simple proportionate adjustment for the appropriate total prevalence treated would give the associated expected costs.

Table 11: Total Cost per Annum of Riluzole in a District of 500,000 Population

PREVALENCE (PER 500,000 pop.)	DRUG COSTS
20	£66,000
30	£99,000
40	£132,000

4. OPTIONS FOR PURCHASERS AND PROVIDERS

Empirical analysis of the 18 month trial data indicates a high cost per life year gained over 18 months for the trial population. However, uncertainty regarding the implications of prognostic factors on survival and uncertainty regarding long-term treatment benefits due to the short duration of the study imply that the long-term cost-effectiveness is likely to be underestimated. In the light of this uncertainty the three options for purchasers are :

Option 1: Do Not Fund the Purchasing of Riluzole.

The published trial demonstrates a reduction in risk of death through the use of riluzole therefore, despite the EMEA's reservations on the use of riluzole, (see Appendix A), ethical arguments may prevent further large scale, long-term clinical trials. Therefore a decision not to fund the provision of riluzole would have to be based on the expectation that further analysis of the trial data would clarify the effects of prognostic and demographic factors on survival and that the experience of other purchasing bodies would clarify the long-term survival patterns associated with riluzole use.

Option 2: Limited Funding of Riluzole

Make riluzole available to patients who satisfy strict clinical criteria and institute mandatory monitoring of long-term patient survival.

The inclusion criteria for the two studies should be used as initial baseline selection criteria; these are detailed further in the following discussion. Further scope exists to identify specific patient sub-groups which would benefit from riluzole treatment. Firstly, a further analysis of the trial data could investigate the benefits achieved in the high and low risk groups identified in the Lacomblez article, (see Figure 2 of that paper).[4] Secondly, a small scale study by Sojka[8] has identified evidence that riluzole may not be uniformly effective for all types of ALS and concludes 'whether there exist subgroups of ALS patients especially suited to riluzole treatment must be settled in further studies.'

Further work would be required to define a protocol for the mandatory monitoring of long-term survival. Due to the low incidence of ALS, monitoring of survival should be co-ordinated over a group of purchasing bodies. The trial results did not indicate a significant effect on functional outcomes. This, together with the low sensitivity of the available functional

outcome measures, implies that such monitoring should focus on mortality or tracheostomy-free survival rather than ALS associated morbidity. Historical survival data, where available, together with the published reviews of long-term survival[6,7,9,10,11] should be used to identify a null treatment survival baseline. Alternatively, a methodology such as that used by Sojka[8] may provide the ability to monitor effects of riluzole on the disease progression rate of individuals.

In addition, purchasing bodies should seek further clarification on the effects of prognostic factors in determining survival benefits; validation of the assumptions made in the analyses presented here would mean that the cost-effectiveness of riluzole treatment would be in line with other funded interventions.

Option 3: Fund Unrestricted Riluzole Use.

The effectiveness of riluzole in extending tracheostomy-free survival has only been identified in the sub-group of people with ALS which satisfied the inclusion criteria for the trial. Benefits in terms of reduced risk of death or tracheostomy have not been proven in the population excluded from the analysis. Furthermore, a double blind placebo controlled study of the use of riluzole in ALS patients who did not fulfil the inclusion criteria for the study was undertaken in parallel to the main Lacomblez study.[4] This study was undertaken on compassionate grounds. The results from this study are unpublished but identify no significant benefit in terms of tracheostomy-free survival arising from the use of 100mg riluzole in this high risk population.

5. DISCUSSION AND CONCLUSION

A review of the statistical analysis presented in the Lacomblez article[4] has been undertaken and is presented in Appendix B. This review supports the validity and appropriateness of that analysis and the claims made for a statistical evidence of dose response relationship between riluzole use and tracheostomy-free survival.

There are, however, considerable difficulties in interpreting the results in a manner which is meaningful when considering the clinical usefulness of treatment and hence when considering whether or not to support the purchase of riluzole. Bensimon in his reply to Guiloff[13] recognises that it is preferable to consider the absolute decrease in event rate rather than the relative risks at a point in time, however, such figures are not provided for the trial results adjusted for prognostic factors. This shortcoming in the paper is compounded by the fact that the published articles are not clear in the description of results, for example, Table 3 of the Lacomblez article[4] and Table IV of the Bryson article[12] refer to survival analysis when the statistics presented are the relative risks (or relative hazards) at the 12 and 18 month time-points. Further, an improvement in median survival of three months has been quoted and attributed to the Bensimon, Lacomblez studies. This claim is not made in the Lacomblez article[4] and is refuted by Bensimon in his reply to the letter by Guiloff.[13] Further, since the survival in the 100mg treatment group does not drop to 50% and the placebo group only reaches 50% at the extreme end of the study, it is not possible to measure the improvement in terms of median survival.

The analysis presented in this report attempts to interpret the published results in a manner which is meaningful for purchasers. This is undertaken through modelling of long-term survival patterns under a range of different assumptions, together with Cox Proportional Hazards modelling of the trial data. It should be noted that some of the published effects of prognostic factors appear to be counter intuitive. For example visual analogue scale (VAS) stiffness and disease duration appear to decrease risk. The disease duration effect could imply that progressive ALS is a heterogeneous group. That is, individuals who have progressed quickly from onset to diagnosis and subsequent inclusion in the trial are more likely to have a rapidly progressing disease, whilst individuals who have a slowly progressing disease are more likely to have a high disease duration at inclusion in the trial. Guiloff[13] quite rightly expresses caution when interpreting such proportional hazards models.
This caution should be redoubled in the light of the long-term survival modelling made necessary by the short duration of the trials. It could be argued that Rhone-Poulenc Rorer

were unethical in allowing the trial to stop before incontrovertible evidence concerning the drug's use over the typical lifespan of the disease was obtained. This, together with the licensing bodies' willingness to approve the drug whilst uncertainties in its use still exist, has put local health authorities in the position of having to make purchasing decisions on minimal information. The intention here has not been to produce an analysis by haphazardly throwing caution to the wind, but rather to extend the published analyses to be able to say something about the likely cost-effectiveness of riluzole given a set of clearly identified assumptions, and hence to support purchasing decision makers. The analysis aims to highlight the potential long-term cost-effectiveness of riluzole, the need for further information from the trial study and the need for further information on long-term survival.

However, the best estimate of cost per life year gained, that is £27,600, is higher than that for many healthcare interventions currently in use, for example the use of "statins" in the secondary prevention of coronary heart disease has a cost per life year gained of £5,100. Haemodialysis for end-stage renal failure, which is widely recognised as a high cost intervention, is more cost effective at around £20,000 per life year gained.

Riluzole treatment for up to 18 months has been shown significantly to increase survival in ALS. Further, since the study[4] appears to be based on a mixed prevalence and incidence population, intuitively one might expect that patients prescribed the drug as they present may derive more benefit than a cohort which would include by definition patients who have progressed markedly with the disease. The manufacturer states that newly or recently diagnosed patients, with more functioning motor neurones available when treatment is initiated, are more likely to benefit from riluzole. Moreover, in an unpublished study of late stage ALS, survival time with riluzole treatment did not differ from placebo. However, although riluzole retards disease progression, it does not appear to arrest the disease and, on current evidence, provides no other objective or subjective improvement. Nevertheless, riluzole is an important step forward in the management of people with ALS, which has hitherto been supportive and palliative. It is currently licensed to extend life or the time to mechanical ventilation in these patients.

It is recommended, therefore, that limited funding is provided for riluzole together with mandatory monitoring. This recommendation is made in the light of the above comments and bearing in mind specifically the inclusion criteria used in the clinical trials and research being undertaken to identify patient sub-groups for treatment. The following criteria should normally be met before offering patients treatment with riluzole:

- A diagnosis of definite or probable ALS made by a consultant neurologist;

- The contra-indications and precautions specified in the 'Summary of Product Characteristics,[14] should apply:
  (a) Patients who have a history of severe hypersensitivity reactions to riluzole or any of the tablet components
  (b) Patients who have hepatic disease or who have baseline transaminases greater than three times the upper limit of normal
  (c) Patients who are pregnant or lactating.

- Treatment should be initiated by a consultant neurologist and only after a frank discussion with the patient;

- Blood tests should be performed monthly for the first three months and, thereafter, every three months to monitor for adverse hepatic effects.

There is no upper age limit for riluzole treatment. Patients in the clinical trials had mean ages in the range 50-60 years, and the oldest patient was 75 years of age. Patients should be in a reasonable state of general health without features of dementia, renal or hepatic dysfunction. It has been suggested that respiratory function should normally show forced vital capacity (FVC) not less than 60% of that predicted for the patient's age and height for treatment to be considered.

6. USE OF RILUZOLE IN THE TREATMENT OF MOTOR NEURONE DISEASE : SUMMARY MATRIX

PATIENT GROUP	PATIENT CRITERIA (GUIDELINES NOT PROTOCOLS)	ESTIMATED FUTURE ACTIVITY	OPPORTUNITY FOR COST SAVING	AUDIT POINTS	EFFECTS THAT COULD BE EXPECTED IN RELATION TO STARTING POINT	COST-EFFECTIVENESS
Patients with ALS/MND.	Patients aged 17-75 with clinically probable or diagnosed ALS. Disease duration no longer than 5 years. Predicted FVC >60%.	Prevalence estimate for all MND is 30 for a district population of 500,000. Annual incidence ranges from 5 - 8 patients.	No comparable treatment. Impact upon use of other health and social services unknown.	Mandatory long-term monitoring of tracheostomy-free survival should be undertaken.	Reduced mortality	The best current estimate of long-term cost-effectiveness ranges from £14,800 to £41,100 with a central estimate of £27,600. The number needed to treat over 18 months is approximately 9. Over a 10 year treatment horizon the estimate ranges from 2 - 7 with a central estimate of four.

APPENDIX A: CONCLUSIONS OF THE COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP) OF THE EUROPEAN AGENCY FOR THE EVALUATION OF MEDICINAL PRODUCTS (EMEA) IN CONSIDERATION OF A MARKETING AUTHORISATION FOR RILUTEK. (CPMP/132/96 - Procedure No. EMEA/H/C/109/00/00)

(Extract from *Committee for Proprietary Medicinal Product's European Public Assessment Report (EPAR) on Rilutek (CPMP/290/96) : International Non-Proprietary Name (INN): Riluzole*. European Agency for the Evaluation of Medicinal Products. 1996 < http://www.eudra.org/emea.html>(9.10.1997)) *

Riluzole has been demonstrated to extend survival in two studies conducted in patients with ALS, but not in a third trial. Survival was the main efficacy criterion and was considered as a strong outcome measure.

The failure to find any effect on functional end-points does not affect the reliability of the survival results.

The survival data obtained with riluzole were analysed at several time-points to explore the robustness of the findings: the general consistency of the findings is of interest, rather than specific achievements of selected significance levels. The consistent outcome of significance levels achieved in the different analyses, together with the higher levels of statistical significance associated with the Cox model, is reassuring.

An effect on functional end-points, if established, would help to support the survival results: however, up to date scores on functional scales are not validated as surrogate markers of survival in ALS.

The CPMP in its meeting on 14 February 1996 adopted by scientific consensus a positive opinion on Rilutek.

The Committee in recommending the granting of a marketing authorisation felt it was important to set out in the 'Summary of Product Characteristics' the results of the clinical trials on which the authorisation was based. The Committee felt that this was particularly important because **treatment with riluzole does not demonstrate a positive effect on functional symptoms of the disease whilst the magnitude of the effect on survival is modest. There are therefore remaining uncertainties on the product in the management of Amyotrophic Lateral Sclerosis.**
The specialist physicians using riluzole will be fully aware of the data.

The therapeutic indication approved is the following:

“Riluzole is indicated to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis (ALS).

Clinical trials have demonstrated that RILUTEK extends survival for patients with ALS.

Survival was defined as patients who were alive, not intubated for mechanical ventilation and tracheotomy-free.

There is no evidence that riluzole exerts a therapeutic effect on motor function, lung function, fasciculations, muscle strength and motor symptoms. Riluzole has not been shown to be effective in the late stages of ALS.

Safety and efficacy of riluzole has only been studied in ALS. Therefore, riluzole should not be used in any other form of motor neurone disease.”

APPENDIX B: ScHARR INTERNAL REVIEW OF STATISTICAL ANALYSIS PRESENTED IN 'DOSE-RANGING STUDY OF RILUZOLE IN AMYOTROPHIC LATERAL SCLEROSIS.' *Lancet* 1996; 347: 1425-31.

Comments on Article

Lacomblez L, Bensimon G, Leigh PN, Guillet P and Meininger V. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. *Lancet* 1996; 347: 1425-31.

The 'Unadjusted Analysis'

The logrank test is a non-parametric method for testing the null hypothesis that the groups being compared are samples from the sample population as regards survival experience. The principle of the logrank test is to divide the survival time scale into intervals according to the distinct observed survival times, ignoring censored survival times. For each time period we compare the observed data (O) with what we would expect (E) if the null hypothesis that there is no real difference between the groups is true.

The logrank test to compare k groups produces for each group an observed (O) and expected (E) number of events. These are compared by calculating the sum of $(O-E)^2/E$, called X^2, and comparing this result to a χ^2 distribution with $k - 1$ degrees of freedom.

The logrank test can be extended to allow an adjustment to be made for other variables. In this paper the subjects are divided or *stratified* into sub-groups according to the site of disease onset. The values of O and E are calculated for each treatment group within each stratum. For each treatment group the values of O and E from each stratum are added up and then these sums are compared using the usual logrank formula to get X^2.

The 'Adjusted Analysis' Modelling Survival - the Cox Regression Model

The logrank test is a non-parametric method for comparing the survival experience of two or more groups. It cannot be used to explore (and adjust for) the effects of several variables (such as age, disease duration, bulbar sign at entry etc.) on survival - for this we need a regression method.

Cox's Proportional Hazards regression analysis (1972) is a 'semi-parametric approach'. No particular type of distribution is assumed for the survival times, but a strong assumption is

made that the effects of different variables on survival are constant over time and are additive in a particular scale (Altman, 1991).

The hazard function represents the risk of dying in a very short time interval after a given time, assuming survival thus far. It can be interpreted, therefore, as the risk of dying at time *t*. Cox's method is similar to multiple regression analysis, except the dependent variable is the hazard at a given time. If we have several variables of interest (e.g. age, disease duration, bulbar signs at entry etc.), we can express the hazard or risk of dying at time *t* as:

$h(t) = h_0(t) \times exp(b_{age}.age + b_{duration}\ duration + ... + b_{N.America}\ N.America).$

The quantity $h_0(t)$ is the baseline or underlying hazard function and corresponds to the hazard when all the variables are zero (because $e^0 = 1$). The regression coefficients b_{age} to $b_{N.America}$ are estimated using the method of maximum likelihood (Collett, 1994) using an appropriate computer program (e.g. SAS or SPSS).

If we have just one variable of interest, e.g. age then: $h(t) = h_0(t) \times exp(b_{age} \times age)$. Under this model a proportionate change in age such as a 50% increase from 40 to 60 years, results in a proportional change in the log of the hazard. This is the reason for the name 'proportional hazards' and the fact that for two cases, the ratio of the hazards will be a constant for all time-points.

The assumption of proportional hazards can and should be tested. This appears to have been carried out in the study, (page 1427, second column, 1st paragraph) although the results are not reported.

The Cox model must be fitted using an appropriate computer program although no name is given in the paper. This program does appear to allow for the stepwise selection of prognostic variables. An appropriate stepwise selection procedure with a significance level of 5% for variable entry in the model appears to have been used.

The value of the riluzole dose ranges from 0 mg (placebo) to 200 mg. In order to guard against the extreme values of this variate having an undue impact on the coefficient of *dose*, natural logarithms have been used in the modelling process. So the riluzole doses (of 50 mg, 100 mg and 200 mg) were transformed by the use of the natural log transformation. E.g. ln(*placebo*) = 1, ln(*50*) = 3.9; ln (*100*) = 4.6; ln(*200*) = 5.3.

The possibility of interactions between the treatment effect and site of onset and countries appears to have been investigated in the study, (page 1427, second column, 1st paragraph) although again the results are not reported.

Interpretation of Model

The final model from a Cox regression analysis will yield an equation for the hazard as a function of several covariates (11 plus treatment variables in this paper- see Table 4). The coefficients of the explanatory variables in the model can be interpreted as logarithms of the ratio of the hazard of death to the baseline hazard.

For continuous covariates (e.g. age, disease duration, weight etc.) the regression coefficient refers to the increase in log hazard for an increase of 1 in the value of the covariate. Thus at 18 months (page 1428, Table 4) the estimated hazard or risk of death increases 1.48 times if a patient is 10 years older, after adjustment for the effects of the other variables in the model.

The above interpretation, assumes that the hazard ratio for an individual aged 70, relative to one aged 60, would be the same as that for an individual aged 30 relative to one aged 20 other things being equal. This linearity assumption can be checked by fitting a factor to the model with levels corresponding to different age bands. There is no written evidence to suggest this has been carried out except for the variate drug dose. However, this does not seem to affect the overall statistical validity of the model.

Similarly, the effect off 50 mg of riluzole is to reduce the hazard to 0.76 of that of the placebo. The overall effect on the survival probability, however, cannot be described simply as it depends on the patient's values of the other variables in the model.

Prognostic Index

The combination of the regression coefficients and values of variables can be used as a prognostic index (PS) or score (page 1428, second column, 1st paragraph).

E.g. *PS = (ln 1.48 x age) + (ln 0.67 x disease duration) + ... + (ln 0.69 x N.America).*

After calculating the PS for all 959 patients, the trial population was split by its median PS into two groups (high and low risks) and Kaplan-Meier survival plots produced for these two new groups (page 1428, Figure 2). Unfortunately, no mention is given of what this median group splitting value was. This omission makes it difficult to estimate the probability of a new patient surviving a given time.

Summary

Overall the article is well written and the appropriate statistical methods have been used. The use of riluzole in this group of amyotrophic lateral sclerosis (ALS) patients has led to an increase in survival without a tracheostomy even after adjustment for prognostic factors. There is strong statistical evidence of a dose-response relationship between the use riluzole and tracheostomy-free survival in this group of patients i.e. increased doses of riluzole lead to longer tracheostomy-free survival.

If this study population is representative of ALS patients, then there is clear evidence that larger doses of riluzole will lead to longer survival. No details are available on the optimum dose for individual ALS patients, although a prognostic scoring index could be calculated for an individual ALS patient which might aid clinical decision making. Finally no information is available on the 'change' in quality of life of the ALS patients given their increased survival. Are we adding life to their years or years to their life?

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14