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Rapid review

The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review

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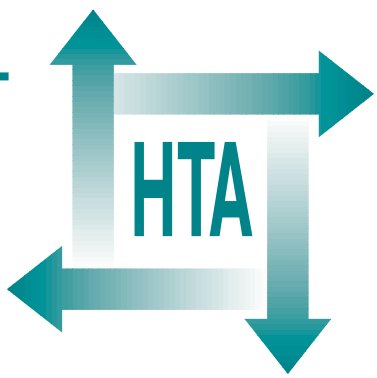
NHS R&D HTA Programme



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The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review

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Contents

List of abbreviations and glossary

ALAT	alanine aminotransferase
ALS	amyotrophic lateral sclerosis (the commonest sort of MND that affects both upper and lower motor neurones, and is characterised by muscle weakness, atrophy, spasticity, brisk reflexes, emotional lability, fasciculation and weight loss)
ASAT	aspartate aminotransferase
asthenia bulbar muscles	subjective sensation of weakness those muscles innervated by nerves originating in the bulbar region of the brain that control the tongue, speech and swallowing
CBA	cost–benefit analysis (attempts to measure all the resource implications and consequences in the same units (usually monetary), to demonstrate whether an intervention is worthwhile)*
CEA	cost-effectiveness analysis (uses a clinical endpoint as a primary measure of outcome, and presents costs and effects for this outcome measure, usually as a cost per adverse clinical event avoided)
CGI	clinical global impression
CI	confidence interval
Cox (proportional hazards) model	regression model for use with survival data, and may be used to construct prognostic indices or produce adjusted analyses. The proportional hazards assumption requires that the relative treatment effect (HR) remains constant over time
CPMP	Committee for Proprietary Medicinal Products
CUA	cost–utility analysis (evaluates the relative importance of each outcome in terms of improvements in length of life and health-related quality of life, expressed as a single measure, such as cost per QALY)
DARE	Database of Abstracts of Reviews of Effectiveness
EMEA	European Medicines Evaluation Agency
EQ-5D	EuroQol quality-of-life measurement instrument
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GOT	glutamic-oxaloacetic transaminase*
GPT	glutamic-pyruvic transaminase*
HA	Health Authority
HR	hazard ratio (summarises the difference between two Kaplan–Meier survival curves, and may be thought of as the overall relative risk of experiencing a critical 'event' (such as death) over the period of follow-up)
ICER	incremental cost-effectiveness ratio
ITT	intention-to-treat
Kaplan–Meier survival curve	graphical summary of the observed survival of one or more groups of patients, based on non-parametric estimates of survival probabilities at each timepoint during follow-up

continued

continued

lower motor neurone	originate in the brain stem or the anterior horn cells of the spinal cord and innervate muscle. Lesions of lower motor neurones cause characteristic signs: muscle atrophy, fasciculation, flaccid weakness, diminished reflexes
motor neurone	nerve cell originating in the brain, brain stem or spinal cord through which movement is initiated or controlled
MND	motor neurone disease (this term is used in two ways generically to cover all diseases that are characterised by degeneration of the motor neurones or to refer to ALS)
NA	not applicable*
NHS EED	NHS Economic Evaluations Database
NICE	National Institute for Clinical Excellence
O-E	one of the Mantel–Haenszel statistics that is the observed minus expected number of deaths (with E calculated by the log-rank method). The log HR(ln[HR]) is estimated by (O – E)/V*
OR	odds ratio
QALY	quality-adjusted life-year (used in CUA)
RCT	randomised controlled trial
SD	standard deviation
SEM	standard error of the mean
sensitivity analysis	investigates how conclusions change when one or more of the inputs varies, and assesses how robust conclusions are to uncertainties, such as varying drug costs or survival
SG	standard gamble
upper motor neurone	originate in the brain (cortico-spinal tract cells), and lesions of these tissues cause characteristic signs: spasticity, stiffness, brisk reflexes, abnormal reflexes (e.g. Babinski reflex), spastic weakness
V	one of the Mantel–Haenszel statistics that is the sum of the hypergeometric variances at each time point where a death occurs*
VAS	visual analogue scale
VC	vital capacity

* Used only in tables and figures

Executive summary

Update

After this review had been completed, the manufacturers of riluzole provided some additional information, which had been requested whilst the report was in preparation. These additional materials are addressed in an update section appended to this report. This summary reflects the information contained in the update.

Background

Riluzole (trade name Rilutek®) is a drug used to treat people with the amyotrophic lateral sclerosis (ALS) form of motor neurone disease (MND). Its licensed indication is to extend life or the time to mechanical ventilation, and it costs about £3700 per year. The prevalence of MND is approximately seven per 100,000, and ALS constitutes 65–85% of this. Incidence rises with age. At any one time, about 3000 people in the UK have ALS, and a district of 500,000 residents could expect to have about 20–25 ALS sufferers.

ALS is a progressive disorder that causes degeneration of the motor neurones of the brain and spinal cord. Symptoms include spasticity, muscle weakness and paralysis and impaired speaking, swallowing and breathing. The disease is extremely distressing for patients and their carers, and is relentlessly progressive with death usually occurring within 3–5 years. Survival time is significantly reduced when the disease starts with bulbar symptoms or at an older age. Death usually occurs from respiratory infection and failure, and complications of immobility. There is no cure and treatment consists mostly of symptomatic, supportive and palliative care.

Objective

To assess the clinical effectiveness and cost-effectiveness of riluzole for the treatment of MND.

Methods

A systematic review of randomised controlled trials (RCTs) and economic studies addressing the clinical effectiveness and cost-effectiveness of riluzole in MND was undertaken. Electronic databases, reference lists from publications, conference abstracts and the Aventis Pharma submission to the National Institute for Clinical Excellence were searched. Clinical experts and specialist organisations were also contacted. Studies were included if they had investigated either clinical effectiveness, cost-effectiveness or safety of riluzole, or quality of life/patient satisfaction associated with its use in MND patients, with no restrictions on age or sex. The review adhered to the guidance of the West Midlands Development and Evaluation Service Handbook and the York Centre for Reviews and Dissemination guidelines, and a model of the cost-effectiveness was developed. An existing economic model was also reviewed in detail; revised estimates from this model are provided in the update section of this report.

Results

RCTs found

Four studies met the inclusion criteria for the clinical effectiveness review. All compared riluzole to placebo; three trials used riluzole at 100 mg daily and one used dosages of 50, 100 and 200 mg daily. Three of the trials had broadly similar eligibility criteria, whereas the fourth recruited patients who were ineligible for one of the other trials and thus used patients who were older or more ill or with a forced vital capacity < 60%. All four trials reported tracheostomy-free survival as a main outcome. Most patients were prevalent, rather than incident, cases.

Evidence on clinical effectiveness

Median follow-up in all trials was 18 months with most patients having follow-up of between 16 and 21 months. Combined results favoured riluzole with a hazard ratio for tracheostomy-free survival of 0.88 (95% confidence interval (CI), 0.75 to 1.02). There was no evidence that the effectiveness of the treatment differed by site of onset. There was also no significant difference in effectiveness in daily dosages of between 50 and 200 mg. There was, however, some evidence of statistical heterogeneity ($p = 0.09$) and, if this

is not due to chance, there is no clear explanation as to why this may have arisen.

Riluzole does not improve symptoms. When data on functional status were combined, a small reduction in the rate of deterioration of functional status was observed, although it was not clear whether this was clinically significant. A large proportion of patients in both groups reported adverse events, but there was little overall difference between riluzole and placebo.

There was no evidence available on treatment outcomes beyond 18 months. All placebo patients were offered riluzole at the end of follow-up, and no longer-term comparative data will thus be available from any of these trials.

Costs and economic analysis

The evidence suggests that current published estimates of the cost-effectiveness of riluzole must be viewed cautiously. Some of the key remaining uncertainties concerning the benefits within the economic analysis are the disease stage(s) in which any survival gain is experienced, the quality-of-life utility weights for ALS health states and the mean gain in life expectancy for patients taking riluzole. It is clear that riluzole is associated with a net increase in costs to the health service, although the magnitude of the increase is difficult to predict accurately.

A more robust estimate of the riluzole-induced gain in life expectancy over the whole disease duration is required to diminish current uncertainties relating to methods of extrapolation beyond observed survival in trials. In our model, base-case incremental cost-effectiveness ratio (ICER) produced a cost per life-year of £39,000 and a cost per quality-adjusted life-year (QALY) of £58,000. A sensitivity analysis indicated that the most optimistic ICER (cost per QALY) is £20,000 and the most pessimistic has riluzole dominated by placebo.

A review of the model presented by the manufacturers of riluzole (based on previously published work) is detailed in the update section of this report. This model was derived from a subset of data from one of the four trials identified in this review. In common with the model we developed, this model is sensitive to the methods used to extrapolate benefit over time. The approach presented by the company produced a base-case ICER of £21,000. An alternative approach, presented in the update section of this report, produced a base-case ICER of £31,500. It was not possible with the information provided to perform a full sensitivity analysis or to empirically address sensitivity to alternative means of deriving model parameters from the clinical data.

Conclusions

There is limited evidence of a modest benefit in tracheostomy-free survival for patients taking riluzole. However, the evidence is restricted and uncertainty remains as to the true benefit of riluzole; the CI is wide and compatible with little or no difference between riluzole and placebo. When costs and the health economic impact are considered when extrapolating survival beyond that observed in trials, the uncertainty about whether the benefits are worth the costs is magnified. Even under the most optimistic assumptions, riluzole at best only postpones death for a few months, and does not preclude the need for supportive care and practical help.

If riluzole were to be made available to all patients in whom it is not contraindicated, the annual cost to the NHS would be about £8.4 million, assuming all these patients wish to take it. Many patients, given accurate information about the benefits and effects of riluzole, may choose not to. Patients should be made aware that riluzole does not cure ALS; accurate patient information is essential.

Recommendations for research

Ideally, reliable evidence from further trials is necessary to answer the many uncertainties that exist. These should include a substantial incident population, with long-term (5-year) survival follow-up, and collection of health economic and quality-of-life data. Further analysis of existing trial data and information from ALS databases may provide additional useful data in the short term.

Chapter 1

Aim and background

Aim of the review

To find and examine existing evidence, in order to evaluate the effectiveness and cost-effectiveness of riluzole in the treatment of motor neurone disease (MND).

Background

- MND is a disorder characterised by degeneration of the motor neurones of the brain and spinal cord.
- Symptoms include spasticity, weakness, paralysis and impairment of speech, swallowing and breathing.
- MND is a rare disease with a prevalence of about seven in 100,000.
- The commonest form of MND is amyotrophic lateral sclerosis (ALS), which accounts for 65–85% of all cases.
- At any one time, there are around 3000 people with diagnosed ALS in the UK.
- There is no cure for ALS – it is relentlessly progressive and death usually occurs within 3–5 years.
- Diagnosis can take more than 16 months from symptom onset.

Nature of MND

MND is characterised by progressive degeneration of the motor neurones of the brain, brain stem or spinal cord. It can affect both upper and lower motor neurones. Upper motor neurones (cortico-spinal tract cells) originate in the brain, and lesions cause characteristic signs, such as spasticity, muscle stiffness, brisk reflexes, abnormal reflexes (e.g. Babinski reflex) and spastic weakness. Lower motor neurones originate in the brain stem or the anterior horn cells of the spinal cord and innervate muscle. Lesions of lower motor neurones cause characteristic signs, such as muscle wasting, muscle fasciculation, flaccid weakness, hypertonia and diminished reflexes.

The classification (*Box 1*)[1] and terminology used to describe the different MNDs is not always clear or consistent. This confusion partly reflects our ignorance of the underlying causes and mechanism of neuronal damage. There is also debate as to the extent to which different syndromes are simply manifestations of the same disease process, and, indeed, whether there are several different disease mechanisms underlying what phenomenologically appears to be the same disease.

BOX 1 Classifications of MNDs from Swash[1]

Idiopathic MNDs
ALS
Progressive bulbar palsy
Progressive muscular atrophy
Primary lateral sclerosis
Familial ALS
Juvenile ALS
Madras MND
Monomelic MND

Toxin-related MNDs
Lathyrism
Konzo
Guamanian ALS

ALS is the commonest form of MND, accounting for 65–85% of all cases of MND.[1] Riluzole is licensed for the treatment of ALS, but not for other variants of MND. ALS is characterised by both upper and lower motor neurone signs. Adult-onset ALS usually starts insidiously with symptoms and signs including stumbling, foot drop, weakened grip, slurred speech, cramp, muscle wasting, twitching and tiredness.[1,2] Other symptoms of MND include muscle stiffness, paralysis, incoordination and impaired speaking, swallowing and breathing.[3]

Following the onset of clinical symptoms, ALS progresses relentlessly. Affected patients usually develop a combination of upper and lower motor neurone signs without sensory involvement, with progressive muscle weakness and wasting usually accompanied by brisk reflexes. The disease can begin in either the bulbar muscles (those involving speaking and swallowing mechanisms) or the spinal muscles (involving the limbs), although both will eventually be involved.[4] Memory, intellect, sensation, external ocular muscles and sphincters are not normally impaired.[5]

Mechanism of action

It is hypothesised that excessive stimulation of glutamate receptors on neurones may cause or play an important role in the destruction of motor neurones in MND.[4] Glutamate is a neurotransmitter that tends to excite motor neurone cells. *In vitro*, riluzole inhibits the release of glutamate, decreases firing of motor neurones induced by glutamate receptor agonists and thus protects cells from glutamate-mediated damage.[27] *In vivo*, it has neuroprotective effects, as well as anticonvulsant and sedative properties.[28] It seems to have a dual mechanism of action: it activates a G-protein-dependent process that leads both to the inhibition of glutamate release and to the blockade of some of the post-synaptic events of the N-methyl D-aspartate receptors, e.g. the mobilisation of calcium.[29]

Licensing

Riluzole is currently the only drug licensed for treating ALS in the UK. The licensed indication of riluzole is "to extend life or the time to mechanical ventilation for patients with amyotrophic lateral sclerosis". The Summary of Product Characteristics recommends that riluzole "should not be used in any other form of motor neurone disease". The Summary of Product Characteristics also suggests that treatment should only be initiated by specialist physicians with experience in the management of MND.[27,30]

Adverse effects

The main caution is history of abnormal hepatic function. It is recommended that serum transaminases be measured before initiation of therapy, and then every month during the first 3 months of therapy, every 3 months for the remainder of the first year of therapy and periodically thereafter.[31] Side-effects include nausea, vomiting, weakness, tachycardia, somnolence, headache, dizziness, vertigo, pain, parasthesia and alterations in liver function tests.[32] Side-effects of dizziness or vertigo may affect performance of skilled tasks, such as driving. Riluzole is contraindicated in patients who have hepatic disease, those who have baseline liver transaminases greater than three times the upper limit of normal or in patients who are pregnant or lactating. Studies at repeated doses in patients with renal impairment have not been conducted and thus the use of riluzole is not recommended in this population. For further information, please refer to the Summary of Product Characteristics.

Cost

The recommended dose is 50 mg twice daily. Riluzole costs £286.00 for 56 × 50 mg tablets.[30] This equates to an approximate annual cost of £3700.

Current service provision and utilisation

Riluzole is the only drug currently licensed for ALS. Apart from this, only supportive and palliative care is currently available for sufferers.[33] A wide range of multidisciplinary health and social services may be required,[34] particularly in the late stages of the disease, and are tailored to suit individual needs. NHS services may include physiotherapy, symptomatic treatment, occupational therapy, speech therapy, mobility aids and district nursing.

- Treatment for MND consists mainly of supportive or palliative care
- Riluzole is the only treatment licensed specifically for ALS
- The use of riluzole is currently permitted by 91% of Health Authorities (HAs) according to those responding to a survey (66% of all HAs responded).

In the late stages, the following interventions may be required:

- enteral feeding (for severe dysphagia)
- domiciliary or hospice care
- ventilation (non-invasive)
- mechanical ventilation/tracheostomy.

As riluzole does not actually cure ALS, it would be adjunctive to normal palliative care.[31] Unless riluzole treatment is discontinued due to adverse events, patients will normally take the drug for the rest of their lives.

Considerable variation exists in the level of riluzole prescribing between different countries.[9,35]

Consultation with clinical experts in the UK revealed anecdotal evidence of substantial variation in prescribing policy between individual HAs. A confidential survey of all HAs in England, Wales and Scotland was therefore undertaken as part of this review. A total of 80 replies were received (out of 104 HAs in England and Wales, plus 15 Health Boards in Scotland), representing a response rate of 67%. Of the responders, seven (9%) prohibited the use of riluzole, 17 (21%) allowed GPs to prescribe it, 19 (24%) allowed GPs to prescribe it

under the direction of a neurologist, 22 (28%) only allowed a neurologist to prescribe it, nine (11%) only allowed its use within a shared care programme, three (4%) had an exceptions procedure to decide on individual cases and three (4%) had not yet agreed a policy on riluzole prescribing. Seven HAs had formulated their own guidelines on its use. Thus, the use of riluzole was allowed by 91% of responding HAs, although one-third did not respond.

A total of 3700 prescriptions for riluzole were dispensed in the community in 1998 (Department of Health, London: personal communication, 21 March 2000). This does not reflect hospital prescribing, for which national figures are not available in the UK.

Total worldwide sales of riluzole were 80 million Euros (approximately £50.2 million) in 1999, which was a 30.3% increase from the previous year.[36] The drug has been registered in over 50 countries, and given to more that 50,000 patients. The current level of annual spending on riluzole in the UK is estimated at about £2.5 million.[21]

Chapter 2
Methods

Review questions

The following questions are addressed in this review by assessing existing evidence:

1. What is the clinical effectiveness of riluzole for the treatment of MND?
2. What is the cost-effectiveness of riluzole for the above indication?

Steering group

The review was carried out under the guidance of a steering group comprising a lead reviewer (AS), a main editor (AB), an information scientist (AFS), a senior advisory reviewer (CH), a medical statistician (JS), a health economist (SB) and a mathematical modeller (PB). All members of the steering group had expertise in different areas of systematic reviewing and experience in producing Development and Evaluation Service reports and other reviews. The steering group met regularly to discuss progress, review drafts and decide direction. Additionally, an advisory group of clinical and statistical experts was contacted, to provide clinical and statistical expertise to the review. Details of this group appear in appendix 1.

General methods

The methods of review generally adhered to the guidance laid out in the West Midlands Development and Evaluation Service Handbook[37] and the York Centre for Reviews and Dissemination guidelines.[38] A protocol for the review was produced, and there were no major departures from this, although the particular importance of patient perspectives became apparent, resulting in the addition of a new section on this topic.

Inclusion criteria

Study design

Randomised controlled trials (RCTs) or quasi-RCTs comparing riluzole with placebo or another treatment for MND. It was decided to rely on the methodology of more robust studies such as RCTs, rather than case-series or cohort studies.

Intervention

Riluzole (trade name Rilutek®).

Population

People with MND, with no restrictions on age or sex.

Outcomes

Any that provided information on the effectiveness, cost-effectiveness or safety of riluzole, or quality of life/patient satisfaction associated with its use.

Method of application

Using the above criteria, two reviewers independently made the inclusion or exclusion decisions. Disagreements were resolved by consensus. Decisions were made independently of the data abstraction and prior to the detailed scrutiny of results.

Search strategy

Papers were identified using:

(i) **Electronic databases**: Cochrane Library (2000 issue 2), MEDLINE (1966–2000), EMBASE (1980–2000), Science Citation Index (1981–2000), National Research Register (2000 issue 1), NHS Economic Evaluations Database (EED), NHS Health Technology Assessment Database, Database of Abstracts of Reviews of Effectiveness (DARE), and various internet search engines. A combination of index terms and text word terms were used in the searches, including antiglutamate, anti-excitotoxic, riluzole, Rilutek, MND, motor neuron(e) disease, ALS and amyotrophic lateral sclerosis. Where appropriate, the strategy for identifying RCTs recommended by the Cochrane Collaboration[39,40] was used.

(ii) **Handsearching the Aventis Pharma submission to the National Institute for Clinical Excellence (NICE)**.

(iii) **Contacting clinical experts and specialist organisations** (listed in appendix 2).

(iv) **Citation lists from obtained references**.
(v) **Conference abstracts** (listed in appendix 3).

Information on cost-effectiveness and quality of life was sought from MEDLINE, NHS EED, NHS Health Technology Assessment Database, DARE, EMBASE and Science Citation Index. There were no language restrictions. The searches were last carried out on 28 June 2000. Further details of the search strategy and results are available from the authors.

Quality assessment strategy

Using a structured form, two reviewers independently assessed the validity of the study design for sample size, duration, randomisation procedure, concealment of allocation, blinding, drop-outs, losses to follow-up, intention-to-treat (ITT) analysis used, comparability of groups at entry and performance bias. The disagreements that occurred were resolved by consensus. Study quality was assessed, and studies were also assigned a quality grade using the Jadad scale.

Data extraction strategy

Two reviewers, using a data extraction form, independently abstracted the data. Disagreements that occurred were resolved by consensus. Data were extracted on the following:

- Details of the **study population** and baseline comparability of intervention and control groups
- Details of the **intervention**, such as drug, dosage, mode of administration, duration of treatment
- Details of the **individual outcomes measured**, such as identification of all outcomes which study protocols state will be measured; the specific measurement tool or data collection method; when, how and by whom the outcome data was collected; drop-outs; cross-overs and losses to follow-up for each outcome
- Details of **the results**, where available, as raw numbers, plus any summary measures with standard deviations (SDs), *p*-values and confidence intervals (CIs) where possible.

Methods of analysis

Clinical effectiveness

All trials included an endpoint of tracheostomy-free survival, i.e. time to tracheostomy or death. The inclusion of tracheostomy as well as death as an 'event' deals with the obvious problem that time of death may be strongly influenced by the use of life support. All trials also included endpoints dealing with functional status. In particular, all trials reported changes in muscle testing scores, the Norris bulbar scale and the Norris limb scale. Details of functional scales (reproduced from a secondary trial report by Lacomblez and co-workers[41]) appear in appendix 4.

Tracheostomy-free survival

For survival data, the appropriate summary statistic is the hazard ratio (HR), which summarises the overall relative risk (of experiencing a critical event) over the period of follow-up of all patients. HRs and associated CIs were extracted from the trial reports, or estimated from the summary data for the Kaplan–Meier survival curves where these were not reported directly (see appendix 5). Pooled estimates were derived using the 'fixed-effects' model.

Functional status

Mean scores and standard error of the means (SEMs) for each scale were extracted from trial reports and combined using the fixed-effects model.

Economic evaluation

A critical appraisal of published economic evaluations of the use of riluzole in ALS was carried out. Given the wide variation in published cost-effectiveness estimates, an original economic evaluation was also conducted, which included both a base-case and a sensitivity analysis. Full details of the methods used are reported in chapter 4.

Chapter 3

Results – clinical effectiveness

Studies identified

Searching yielded a total of 298 separate references, excluding duplications, of which 231 were from electronic databases. Many individual references were identified by more than one database. Four RCTs were found that met the inclusion criteria for this review.[42–45] Eight further papers[46–53] that were possibly eligible based on their titles and abstracts were examined, but excluded for reasons explained below. None of the excluded studies were RCTs. Three previous systematic reviews were also identified,[31,54,55] which are summarised in appendix 6.

As well as identifying studies and systematic reviews on the clinical effectiveness of riluzole, other references were found, including studies of other drugs for ALS, non-clinical effectiveness studies of riluzole, non-systematic reviews, background information on riluzole and MND, health economic studies (discussed later in chapter 4) and conference proceedings.

We are aware of the existence of 50-month survival data for the trial by Lacomblez and colleagues,[43] but, although Aventis agreed to provide this,[56] it had not been received by the submission date for this review. We are also aware that an individual patient data meta-analysis of the four RCTs that we identified has been conducted, but not published in full.

Update: both of the above items were received from the company after this report was completed. The new data are addressed in the update section at the end of the report.

Excluded studies

The study by Riviere and co-workers (1998)[46] re-analysed previous trial data, and was therefore excluded. Trials by Sojka and colleagues (1997),[47] Kalra and colleagues (1998),[48] Gawel (unpublished; 1999),[49] Desiato and co-workers (1999)[51] and Couratier and co-workers (2000)[53] were excluded because subjects were not randomised. The trials by Arrida-Mendicoa and colleagues (1999)[50] and Pongratz and co-workers (1999)[52] were excluded because they did not use controls. The excluded trials are summarised in appendix 7.

Included trials

Four trials on the effectiveness of riluzole met all of the inclusion criteria. These were Bensimon and colleagues (1994),[42] Lacomblez and colleagues (1996),[43] Meininger and co-workers (1995)[44] and Yanagisawa and colleagues (1997).[45] Authorship of each of the first three trials was very similar, reflecting the close inter-relationship between these trials.

The number of patients included in the trials totalled 1477. These were recruited mainly from the prevalent population rather than incident, i.e. midway through the course of the disease rather than at its onset. Of these, 503 patients were randomised to placebo and 974 to riluzole (493 at 100 mg per day).

The trial by Meininger and co-workers[44] is an unpublished study, and Yanagisawa and co-workers[45] is in Japanese. The former was included in only one previous systematic review and the latter by none. A meta-analysis using individual patient data from all four of these trials has been carried out by the manufacturer, and reported in a European Public Assessment Report,[57] although it is otherwise unpublished.

Update: results of this meta-analysis were received from the company after this review was completed. The new data are addressed in the update section at the end of this report.

Overview of included trials

Interventions and comparators

Each trial compared riluzole to placebo. Three of the trials used riluzole at 100 mg per day, while the fourth was a dose-ranging study using dosages of 50, 100 and 200 mg per day. A summary of interventions and comparators appears in *Table 1*.

Trial characteristics

All of the four trials were RCTs. Three trials had similar inclusion and exclusion criteria; the main differences were that Bensimon and colleagues[42] and Lacomblez and colleagues[43] excluded patients with greater than 5 years prior duration of disease or forced vital capacity (FVC) less than 60%, whilst

TABLE 1 *Summary of trial characterstics*

	Bensimon *et al.*[42]	**Lacomblez *et al.*[43]**	**Meininger *et al.*[44]**	**Yanagisawa *et al.*[45]**
Intervention	Riluzole 100 mg daily	Riluzole 50 mg daily Riluzole 100 mg daily Riluzole 200 mg daily	Riluzole 100 mg daily	Riluzole 100 mg daily
Comparator	Placebo	Placebo	Placebo	Placebo
Design	RCT	RCT	RCT	RCT
Country	France, Belgium	France, Belgium, Germany, Spain, UK, USA, Canada	France, Belgium	Japan
Number of centres	6	30	10	48
Number patients randomised	155	959	168	195
Number placebo/ riluzole patients	78/77	242/717 Riluzole 50 mg 237 Riluzole 100 mg 236 Riluzole 200 mg 244	86/82	97/98
Inclusion criteria	– Outpatients aged 20–70 – Probable/ definite ALS – ≤ 5 years since first symptoms – ≥ 60% predicted FVC	– Aged 18–75 – Probable/definite ALS – ≤ 5 years duration – ≥ 60% predicted FVC – ALAT[a] and ASAT[b] ≤ twice normal limits	One or more of the following: – Outpatients aged > 75 – Probable/definite limb or bulbar ALS – > 5 years duration – < 40% predicted FVC – Able to understand and give informed consent – Only lower motor neurone signs	– Aged 20–75 – Probable/definite ALS – FVC deterioration < 40% in last 2 months – Informed consent – Ambulatory – Able to tolerate riluzole
Exclusion criteria	– Tracheostomy – Incapacity or life-threatening disease – Hepatic or renal dysfunction – Pregnancy – Signs of conduction blocks of motor or sensory nerves – Signs of dementia – Substantial lesions – Immunoelectro-phoresis – Paraproteinuria	– Tracheostomy – Other life-threatening or incapacitating disease – Renal dysfunction – Pregnancy	– Tracheostomy present/expected ≤ 2 months – Serious illness or handicap – On hepatoxic drug – Multiple conduction block – Signs of dementia/ major psychiatric illness – ALAT[a] or ASAT[b] > twice normal limits – Creatinine plasma > 200 μm/l	– Need tracheostomy in next 6 months – Serious disease affecting prognosis – Renal insufficiency – Renal drugs – Pregnancy – Conduction block – Dementia/ psychiatric disorder – GOT[c]/GPT[d] ≥ twice upper normal limits – Physician's opinion
Duration of follow-up	483–632 days (median 548)	442–548 (cut-off) days (median 548)	548 (cut-off) days (median 548)	Maximum 630 days (median 548)
Censored at:	End of follow-up	18 months		End of follow-up
Reporting intervals (months)	0, 3, 6, 9, 12, 15, 18, 21	0, 3, 6, 9, 12, 15, 18	0, 3, 6, 9, 12, 15, 18	0, 3, 6, 9, 12, 15, 18, 21

[a] *ALAT, alanine aminotransferase*
[b] *ASAT, aspartate aminotransferase*
[c] *GOT, glutamic-oxaloacetic transaminase*
[d] *GPT, glutamic-pyruvic transaminase*

Yanagisawa and co-workers[45] required an 'event-free' life expectancy of at least 6 months and excluded patients whose FVC had decreased by more than 40% during the 2 months prior to randomisation. The trial by Meininger and co-workers[44] was designed specifically for those patients excluded from the Lacomblez trial, which was run in parallel.

Duration of follow-up varied, ranging from 16 to 21 months, and all trials had a median follow-up of 18 months. All surviving patients were censored at 18 months by the Lacomblez and Meininger trials, and to end of follow-up by both Bensimon and Yanagisawa.

At the end of each study, all surviving patients were offered riluzole. Long-term comparative follow-up data will thus never be available (see *Table 1* for trial characteristics).

Validity

All of the four trials were randomised and described as double-blind, and ITT analysis was used in all trials. There was clear definition of patient groups, adverse events were reported and outcomes clearly defined.

The randomisation method was described in all but one trial (Meininger and colleagues, unpublished). It was not always clear whether treatment was masked from investigators. The number of protocol violations varied widely, although none were reported by Meininger and colleagues. A Jadad score was calculated for each trial (*Table 2*), which gives an indication of a trial's quality,

TABLE 2 *Validity of included trials*

	Bensimon *et al.*[42]		**Lacomblez *et al.*[43]**		**Meininger *et al.*[44]**		**Yanagisawa *et al.*[45]**	
Randomised?	Yes		Yes		Yes		Yes	
Randomisation method described?	Yes		Yes		No		Yes	
Double-blind?	Yes		Yes		Yes		Yes	
Treatment masked from patients?	Yes		Yes		Yes		Yes	
Treatment masked from investigators?	Unsure		Yes		Unsure		Yes	
ITT analysis used?	Yes		Yes		Yes		Yes	
Clear definition of patient groups?	Yes		Yes		Yes		Yes	
Loss to follow-up reported?	Yes		Yes		No		Yes	
Adverse events reported?	Yes		Yes		Yes		Yes	
Outcomes clearly defined?	Yes		Yes		Yes		Yes	
Jadad score	4		5		3		5	
Number of protocol violations:								
Placebo	13		7		Not reported		1	
Riluzole	11		28		Not reported		0	
True loss to follow-up:								
Overall	0		9		Not reported		24	
Placebo	0		Not reported		Not reported		14	
Riluzole	0		Not reported		Not reported		10	
Number censored[a] for survival (%):								
No. of months:	12	18	12	18	12	18	12	18
Placebo	0 (0)	14 (18)	1 (< 1)	81 (33)	0 (0)	1 (1)	1 (1)	22 (23)
Riluzole	0 (0)	15 (19)	5 (< 1)	251 (35)[b]	0 (0)	2 (2)	1 (1)	20 (20)

[a] *Censored patients were those who were known to be alive at the last point of contact*
[b] *All riluzole doses combined*

taking aspects of its design and reporting into account. The score ranges from 0 (lowest) to 5 (highest). The trial by Meininger and colleagues had a Jadad score of 3, which may simply be a reflection of the format in which the data were available to us. It seems unlikely that this trial, run in parallel with and by the same investigators as Lacomblez and co-workers would have been designed and conducted to a lower standard.

The majority of patients in all trials were followed for survival endpoints for a period of 18–21 months (the maximum duration of the trials) and very few were censored before 15 months. The relatively large number of patients censored before 18 months in the trial by Lacomblez and colleagues was due to the fact that this trial started later in some countries, thus some patients had been randomised for less than 18 months at the time of analysis. The validity of included trials is summarised in *Table 2*.

Patient baseline characteristics

The ratio of placebo patients:riluzole patients was approximately 1:1, except for the study by Lacomblez and colleagues, which used three treatment arms. As would be expected, there was a slightly higher proportion of males, except in the trial by Meininger and co-workers. The percentage of patients with bulbar onset was generally similar across trials, although somewhat lower in the trial by Bensimon and co-workers. Differences in eligibility criteria for the Meininger study resulted in corresponding differences in predicted FVC, age, duration of illness and weight in this trial, compared to the other three. There was also a greater difference in age between placebo and riluzole in the Meininger trial compared to the other trials. A summary of patient baseline characteristics appears in *Table 3*.

Primary and secondary outcome measures

All trials reported tracheostomy-free survival (time to tracheostomy or death), rather than death alone, as a primary outcome, although the main endpoint in the trial by Yanagisawa and co-workers[45] was progression-free survival. All trials used similar definitions of tracheostomy-free survival, although Lacomblez and colleagues[43] and Meininger and colleagues[44] included intubation, and Yanagisawa and co-workers[45] included dependence on a respirator, as 'events' in their definitions.

Other outcomes included muscle strength, functional status, respiratory function, patients' subjective evaluation of symptoms, clinical global impression and adverse events. Bensimon and co-workers[42] defined measures of functional status as primary outcomes, whereas these were secondary outcomes in the later trials. All trials appear to have used similar scales for assessing muscle strength and limb and bulbar function. Primary and secondary outcomes are summarised in *Table 4*.

Clinical effectiveness

Update: a report of an unpublished meta-analysis based on individual patient data from all four trials was received from the company after this review was completed. The new data are addressed in the update section at the end of the report.

Tracheostomy-free survival

- Results for tracheostomy-free survival by ITT were available from three of the four trials (1282 patients of a total of 1477).
- There is some evidence of a small survival benefit in favour of riluzole, with a pooled HR of 0.83 (95% CI, 0.69 to 0.99).
- There is no clear evidence of statistical heterogeneity between the trials, although there is limited power to investigate this.
- There is some clinical heterogeneity, as one of the trials recruited a somewhat different patient group from the other three trials; considering only the two trials with data available and which recruited similar patient groups had no substantial influence on the overall results.
- There is no clear evidence that the treatment effect differs according to site of disease onset.
- It has been suggested that the benefit of riluzole may be confined to higher-risk patients, but there is insufficient data available to examine the treatment effect according to 'risk'.
- One trial examined different dosages of riluzole (50, 100 and 200 mg), but there is no evidence of a difference in effectiveness between these three dosages.

Definition of endpoint

Survival data is concerned with the time to the first occurrence of one or more critical events. Events for tracheostomy-free survival were defined by the different authors as follows:

> "death (from any cause) and tracheostomy, since in the terminal stage of the disease respiratory failure leads to either event" [42]

> "death (from any cause), tracheostomy, and intubation with artificial ventilation leading to tracheostomy"[43]

TABLE 3 *Summary of patient baseline characteristics*

	Bensimon *et al.*[42]	Lacomblez *et al.*[43]	Meininger *et al.*[44]	Yanagisawa *et al.*[45]
Number patients randomised	155	959	168	195
Number placebo/ riluzole patients	78/77	242/717	86/82	97/98
Number male/ female (% male)	91/64 (59)	575/384 (60)	82/86 (49)	109/86 (56)
Those with bulbar onset:				
Overall	21%	31%	33%	29%
Placebo	22%	Not reported	33%	29%
Riluzole	19%	Not reported	35%	29%
Those with familial form of ALS	Not reported	4%	9%	Not reported
Mean % predicted FVC:				
Overall	Not reported	88.2 (SD 18.9)	53.7 (SEM 2.0)	Only mean FVC stated, not % predicted
Placebo	86 (SD 18)	87.6 (SD 18.2)	55.1 (SEM 2.6)	
Riluzole	92 (SD 17)	50 mg 88.6 (SD 18.9) 100 mg 88.4 (SD 19.1) 200 mg 88.2 (SD 19.4)	51.9 (SEM 3.1)	
Mean age:				
Overall	Not reported	56.7 (SD 11.0)	60.4 (SEM 1.0)	Not reported
Placebo	58.1 (SD 11.0)	56.0 (SD 11.5)	62.8 (SEM 1.4)	58.4 (SD 10.1)
Riluzole	56.8 (SD 11.0)	50 mg 57.1 (SD 10.7) 100 mg 56.9 (SD 10.9) 200 mg 56.8 (SD 10.8)	57.8 (SEM 1.4)	59.6 (SD 9.1)
Mean years duration:				
Overall	Not reported	1.8 (SD 1.3)	3.6 (SEM 0.2)	Not reported
Placebo	2.3 (SD 1.8)	1.8 (SD 1.4)	3.9 (SEM 0.4)	2.5 (SD 2.1)
Riluzole	2.2 (SD 1.7)	50 mg 1.9 (SD 1.2) 100 mg 1.7 (SD 1.2) 200 mg 1.8 (SD 1.2)	3.4 (SEM 0.2)	2.1 (SD 2.0)
Mean baseline weight:				
Overall	Not reported	67.7 (SD 12.7)	60.8 (SEM 1.0)	Not reported
Placebo	65.1 (SD 12)	68.1 (SD 13.1)	61.8 (SEM 1.4)	Not reported
Riluzole	66.0 (SD 12)	50 mg 67.6 (SD 13.0) 100 mg 68.1 (SD 13.4) 200 mg 67.1 (SD 11.5)	59.7 (SEM 1.4)	Not reported

"death, tracheostomy or intubation"[44]

"tracheostomy; dependent on respirator; death"[45] (note that the main endpoint for this trial was progression-free survival, which also included loss of independent ambulation, loss of upper extremities function and tube nutrition as events; tracheostomy-free survival was included as an endpoint in this trial for the purpose of comparison with the earlier European trials by Bensimon and Lacomblez)

Data available

The report of Yanagisawa and co-workers[45] gives no numerical data for the ITT analysis of tracheostomy-free survival. The other three trial reports all give at least one HR and an associated 95% CI relating to a number of different (ITT) analyses of tracheostomy-free survival. For some analyses, only a *p*-value was given, and, in all cases, this was for the log-rank test. The information available from the trial reports is shown in *Table 5*.

In addition, each trial report gives a number of Kaplan–Meier survival curves with summary data at 3-month intervals. This data may be used to approximate the HR and an associated 95% CI (see appendix 5). The information available from the papers, directly and approximated from the

TABLE 4 *Primary and secondary outcomes*

	Bensimon *et al.*[42]	Lacomblez *et al.*[43]	Meininger *et al.*[44]	Yanagisawa *et al.*[45]
Primary outcomes	Tracheostomy-free survival (time to death or tracheostomy) Changes in functional status after 12 months of treatment (Norris limb and bulbar)	Tracheostomy-free survival (time to death, tracheostomy or intubation)	Tracheostomy-free survival (time to death, tracheostomy or intubation)	Progression-free survival (time to death, tube nutrition, dependence on respirator, loss of upper extremity function, independent ambulation, tracheostomy) Tracheostomy-free survival (time to death, tracheostomy or dependence on respirator) Overall survival
Secondary outcomes	Muscle-testing scores Respiratory function Clinical global impression of change scale Patient's subjective evaluations	Muscle strength Functional status (Norris limb and bulbar) Respiratory function Clinical global impression Patient's subjective evaluations	Muscle testing Functional status (Norris limb and bulbar) Safety variables – adverse events, vital signs, electrocardiogram, physical examination, haematology, serum chemistry	Muscle strength Japanese Norris scales (limb and bulbar) Grip Back extension Pinch FVC Safety

TABLE 5 *Tracheostomy-free survival results reported in included trials*

Results reported for tracheostomy-free survival	**Bensimon *et al.*[42]**	**Lacomblez *et al.*[43]**	**Meininger *et al.*[44]**	**Yanagisawa *et al.*[45]**
All patients:				
Unadjusted	*p*-value only	Not reported	HRs and CIs[a]	No data reported[c]
Stratified by site of onset	Not reported	HRs and CIs	Not reported[b]	No data reported[c]
Adjusted (Cox model)	HRs and CIs	HRs and CIs	HRs and CIs	No data reported[c]
Bulbar onset only:				
Unadjusted	*p*-value only	Not reported	HRs and CIs	No data reported[c]
Adjusted (Cox model)	Not done	Not done	HRs and CIs	No data reported[c]
Limb onset only:				
Unadjusted	*p*-value only	Not reported	HRs and CIs	No data reported[c,d]
Adjusted (Cox model)	Not done	Not done	HRs and CIs	No data reported[c,d]

[a] *Not clear if main result was stratified by site or not*
[b] *Not directly reported, but calculable from directly reported results given by site*
[c] *Results reported in text with no numerical information*
[d] *Limb patients in Yanagisawa split into 'early' and 'advanced' disease*

summary data on the survival curves, is summarised in appendix 8.

All trials used a dose of 100 mg daily of riluzole, but the Lacomblez trial also included comparisons with 50 and 200 mg. The results for each of these dosage levels are summarised in appendix 8. There is no evidence from these data of any difference in effectiveness between the different dosage levels (see appendix 9 for discussion), and pooled estimates have, therefore, been used for the three riluzole arms in the Lacomblez trial. The alternative would be to exclude data from the large number of patients receiving riluzole at dosages other than 100 mg, which would ignore a substantial proportion of the available randomised evidence (481 patients of the 1477 randomised in these trials), reducing the precision of the estimate from this trial and of the pooled estimates.

Results (tracheostomy-free survival)

No summary data for tracheostomy-free survival is available from the Yanagisawa trial.[45] Although this endpoint was reported in the text, no numerical data or survival curves are given. The primary endpoint for this trial was progression-free survival, and survival curves are given for this endpoint (see appendix 8). For tracheostomy-free survival, the authors simply note that, "there were also no significant differences between the treatment groups in this [ITT] analysis using death, tracheostomy or artificial ventilation".

Update: the tracheostomy-free survival results of the Yanagisawa trial are included in a report of an unpublished meta-analysis, which was received from the company after this review was completed. The new data are addressed in the update section at the end of the report.

The results for tracheostomy-free survival for the other three trials are summarised in *Figure 1*. There is some evidence of a modest survival benefit in favour of riluzole. The combined HR (from the three trials where data is available) is 0.83 (95% CI, 0.69 to 0.99). Estimates stratified by site of onset are similar to the unadjusted estimates, with an estimated HR of 0.83 (95% CI, 0.70 to 0.98). It is unlikely that the addition of the results from the small Yanagisawa trial would substantially alter these results. Although these data could not be obtained, they were included in an update of a meta-analysis based on individual patient data performed by Rhône-Poulenc Rorer for the European Medicines Evaluation Agency (EMEA) (the other data in this meta-analysis were those from the Bensimon, Lacomblez (100 mg group only) and Meininger trials). When the Japanese data were added to the data from the three European trials, the Committee for Proprietary Medicinal Products (CPMP) concluded that, "…the statistical evidence for the efficacy of riluzole is less secure. Nevertheless…the balance of probability is still in favour of riluzole".

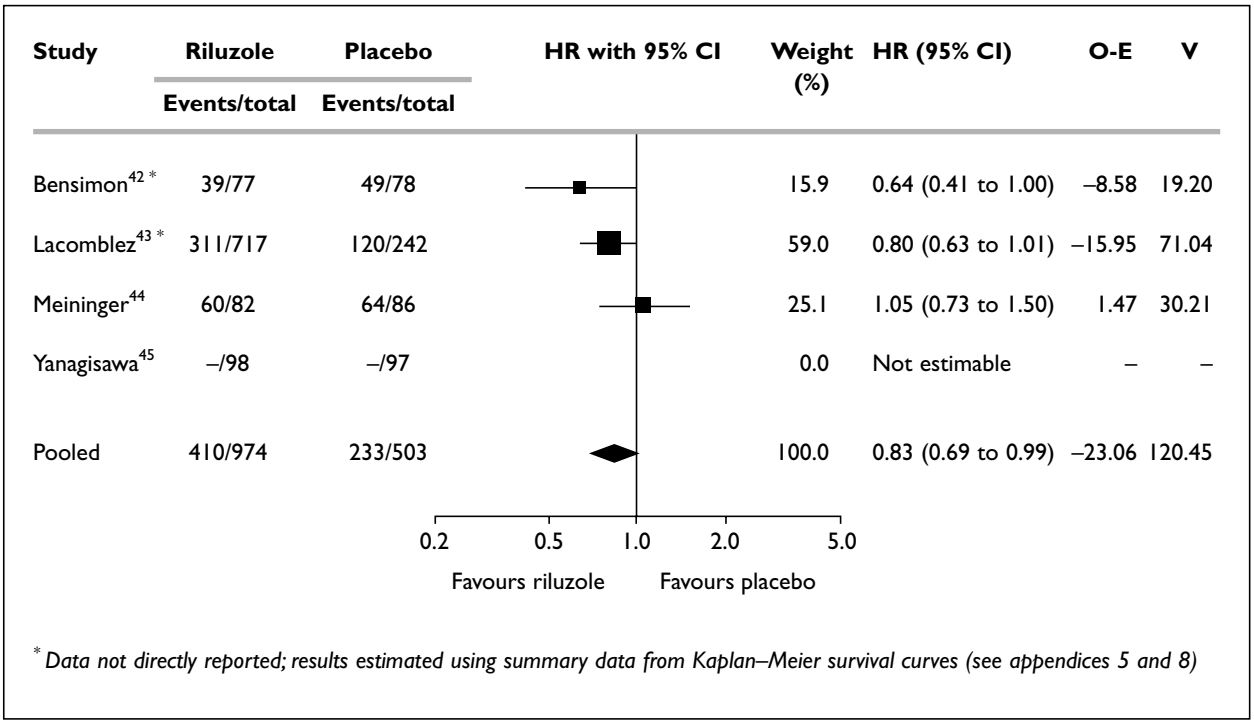


FIGURE 1 *Tracheostomy-free survival (unadjusted results)*

Adjusted analyses

All trials used the Cox proportional hazards model to perform adjusted analyses, although the Yanagisawa report does not give any detail of the model used or the results. Unlike regression approaches with continuous outcome measures, the Cox model does not improve precision, and parameter estimates may be sensitive to violation of the proportional hazards assumption.[58] Although the Lacomblez paper does report an attempt to check this assumption, the available tests of proportional hazards are not powerful and a much larger sample size would be required to detect even quite substantial departures from proportionality.

It is not clear from any of the papers whether there was a pre-specified list of covariates to be included in the adjusted analyses, or whether any covariates initially included were discarded from the model. Bensimon and co-workers[42] and Lacomblez and colleagues[43] both appear to have performed the adjusted analysis alongside construction of a prognostic index, but do not give details of how these models were developed. Only the Meininger report includes 'non-significant' covariates in the report of this analysis. For the Lacomblez data, however, the EMEA did request the results of the Cox model including all pre-specified covariates and noted that, "as was anticipated, the *p*-values were less extreme (50 mg, $p = 0.082$; 100 mg, $p = 0.003$; 200 mg, $p = 0.001$) but the levels of significance attached to the higher dose levels remained high".

The covariates used in the adjusted analyses differed across the trials (see appendix 8). The results of the adjusted analyses are thus not strictly comparable, as parameter estimates may be markedly affected by the inclusion or exclusion of other covariates. The results of these analyses have, therefore, not been formally combined. The adjusted results for each trial are summarised in appendix 8.

None of the adjusted analyses reported differ substantially from the unadjusted results, or results stratified by site of onset. The largest difference due to adjustment is reported by Lacomblez and colleagues.[43] This is, perhaps, surprising given that this is the largest trial with no apparent imbalances in patient characteristics at baseline, although even small differences in factors that are strongly prognostic could be responsible for such an effect. Uncertainties in model selection could also be responsible, although the EMEA did request a further adjusted analysis using direct stratification by risk factors in which "similar levels of significance were achieved". Even if comparable adjusted analyses were available for all trials, it is unlikely that the pooled estimate from these analyses would be substantially (or practically) different from the unadjusted estimates reported above.

Update: adjusted analysis of the data from all four trials was included in a report of an unpublished meta-analysis, which was received from the company after this review was completed. The new data are addressed in the update section at the end of the report.

Timepoint for analysis and treatment effect over time

The results reported above are those for the entire period of follow-up reported for each trial, which was 18–21 months in each case. Bensimon and colleagues[42] state that their primary endpoint was survival at 12 months from randomisation, although they continued to follow-up patients after this time and report all data available up to 21 months from the start of the trial (at which point all placebo patients were offered riluzole). They note that the survival benefit appeared to be greater at 12 months than overall.

Lacomblez and co-workers[43] also reported results at 12 months as well as overall, as they wished to examine the possibility, raised by the Bensimon data, that the treatment effect was greater in the first year from randomisation and, additionally, to check the proportional hazards assumption underlying the use of the Cox model. They also reported apparently greater benefit at 12 months, but the test for interaction by time was not significant. A much larger trial would be required to detect realistic differences in treatment effect over time, and this analysis is thus far from conclusive.

Comparison of HRs over different time periods may be useful, particularly for examining the assumption of proportional hazards (as performed by Lacomblez and co-workers[41]). A particular period of follow-up is implicit in power calculations for survival analysis because the 'effective sample size' is dependent on the number of events observed, and is thus a function of both the number of patients randomised and the period over which they are followed up. However, methods for analysing survival data are designed specifically to deal with variable follow-up times, i.e. to account for censored data. Unless there is a very clear *a priori* rationale, it is inappropriate (and wasteful) to emphasise survival results at a particular timepoint rather than using all data available from the entire period of follow-up. The HR for the full data set, along with the Kaplan–Meier survival curves,

provides the most appropriate and reliable summary of treatment effects in the patient population recruited to the trial.

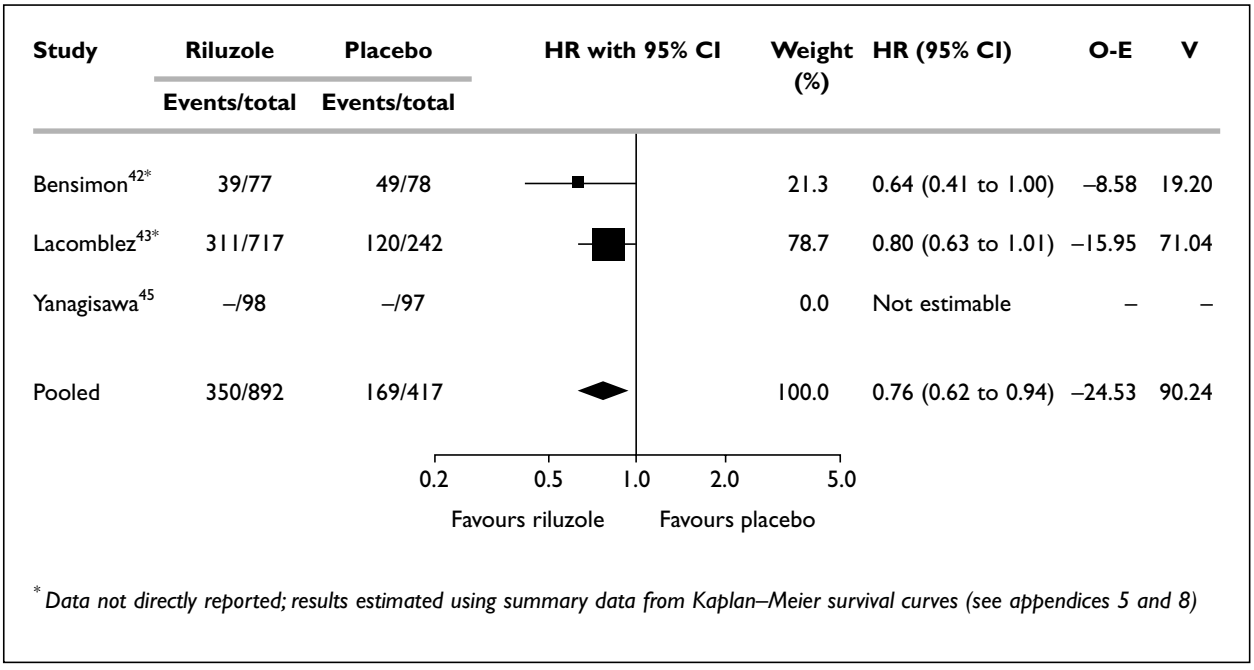
For these trials, it is, perhaps, worth examining the implications of this approach compared to an analysis based on data at 12 months. Both Bensimon and Lacomblez report somewhat more favourable results at 12 months, although neither report gives undue emphasis to this result compared to the longer-term data. The combined data from these trials is insufficient to allow any clear statement about changes in treatment effect over time. If it is assumed that there is, in fact, no difference in long-term compared to short-term effects, then the longer-term result gives a more reliable estimate of the true treatment effect, and is thus preferred. If, on the other hand, it is assumed that any benefit does, in fact, decrease with time, then results based on short-term data are misleading because they do not reflect the experience of patients who live (are event-free) beyond this timepoint. It is worth noting that if short-term benefit is high compared to the benefit overall (survival curves are 'banana-shaped' and converge rapidly) then the total gain may be less than that obtainable if the overall benefit were smaller but constant over time (survival curves are more like a ski-slope and remain separated for longer).

The 12-month data have, therefore, not been summarised because the overall results are more reliable, more informative and thus more appropriate. Although it might have been advantageous to examine the possible dependence of treatment effect on time, it has not been possible to do this due to the small numbers of patients randomised and the lack of long-term follow-up. Unfortunately, placebo patients in these trials were offered riluzole at the end of follow-up (16–21 months), and, therefore, even if it were available, additional, long-term comparative data from these trials would be difficult to interpret.

Heterogeneity

There is no significant statistical heterogeneity in these results, and the addition of the results from the Yanagisawa trial is unlikely to substantially increase heterogeneity. However, the test for (statistical) heterogeneity is not particularly powerful, and the results from both the Meininger and Yanagisawa trials, although small, are somewhat discordant with the Bensimon and Lacomblez data.

There is some clinical heterogeneity between the trials. In particular, Meininger recruited a very different patient population from the other trials. This trial was run in parallel with the Lacomblez trial and entry criteria were essentially defined as ineligibility for the Lacomblez trial. The Meininger trial thus included patients who were older than 75 or with > 5 years prior duration of disease or with an FVC < 40%. In order to investigate the impact of this trial on the pooled results, the analysis was repeated excluding this trial (see *Figure 2*).



* *Data not directly reported; results estimated using summary data from Kaplan–Meier survival curves (see appendices 5 and 8)*

FIGURE 2 *Results excluding Meininger trial*

Although the Meininger trial was 'negative', it was a small trial and its exclusion had no substantial impact on the pooled results; the pooled HR from Bensimon and Lacomblez combined is 0.76 (95% CI, 0.62 to 0.94). As before, the results stratified by site of onset are similar, with a pooled HR of 0.78 (95% CI, 0.65 to 0.94). It is unlikely that inclusion of the results from the Yanagisawa trial, although also 'negative', would have a substantial practical impact on these results either.

There is thus **some** evidence that riluzole confers a small survival benefit in the patient group recruited to the Bensimon and Lacomblez trials. These patients were similar to those recruited to the Yanagisawa trial; there are no substantial differences apparent in the reported patient characteristics between these three trials. There is no evidence of a benefit for the group with generally more advanced disease excluded from these trials but included in the Meininger trial. However, this is a lack of evidence, due to the small size of this trial, and the results cannot be interpreted as evidence of no benefit in this (somewhat heterogeneous) group.

Update: the tracheostomy-free survival results of the Yanagisawa trial are included in a report of an unpublished meta-analysis, which was received from the company after this review was completed. The new data are addressed in the update section at the end of the report.

Treatment effect in subgroups – effect by site of onset

All four trials investigated subgroups by site of onset (bulbar and limb). Bensimon and colleagues[42] report a (quantitative) difference in treatment effect between the two groups, although it is not clear what methods (if any) were used to investigate the interaction. The authors note that their results show a substantial benefit in favour of riluzole for patients with bulbar onset but little apparent benefit for those with limb onset.

Following the report of Bensimon and co-workers,[42] the confirmatory trial by Lacomblez and colleagues[43] also investigated the possibility of an interaction between treatment and site of onset, using a much larger data set. They reported that there was no significant interaction ($p = 0.62$, using the Cox proportional hazards model), and, for this reason, they did not report results separately for the two groups.

Meininger and co-workers[44] report a significant (qualitative) interaction between treatment and site of onset ($p < 0.01$, using the Cox proportional hazards model). Examination of the treatment effect within groups indicated a moderate benefit associated with riluzole in patients with limb onset and a substantial detriment in those with bulbar onset. Note that the direction of the interaction reported here was the opposite to that reported by Bensimon and co-workers, who found riluzole to be of greatest benefit for patients with bulbar onset.

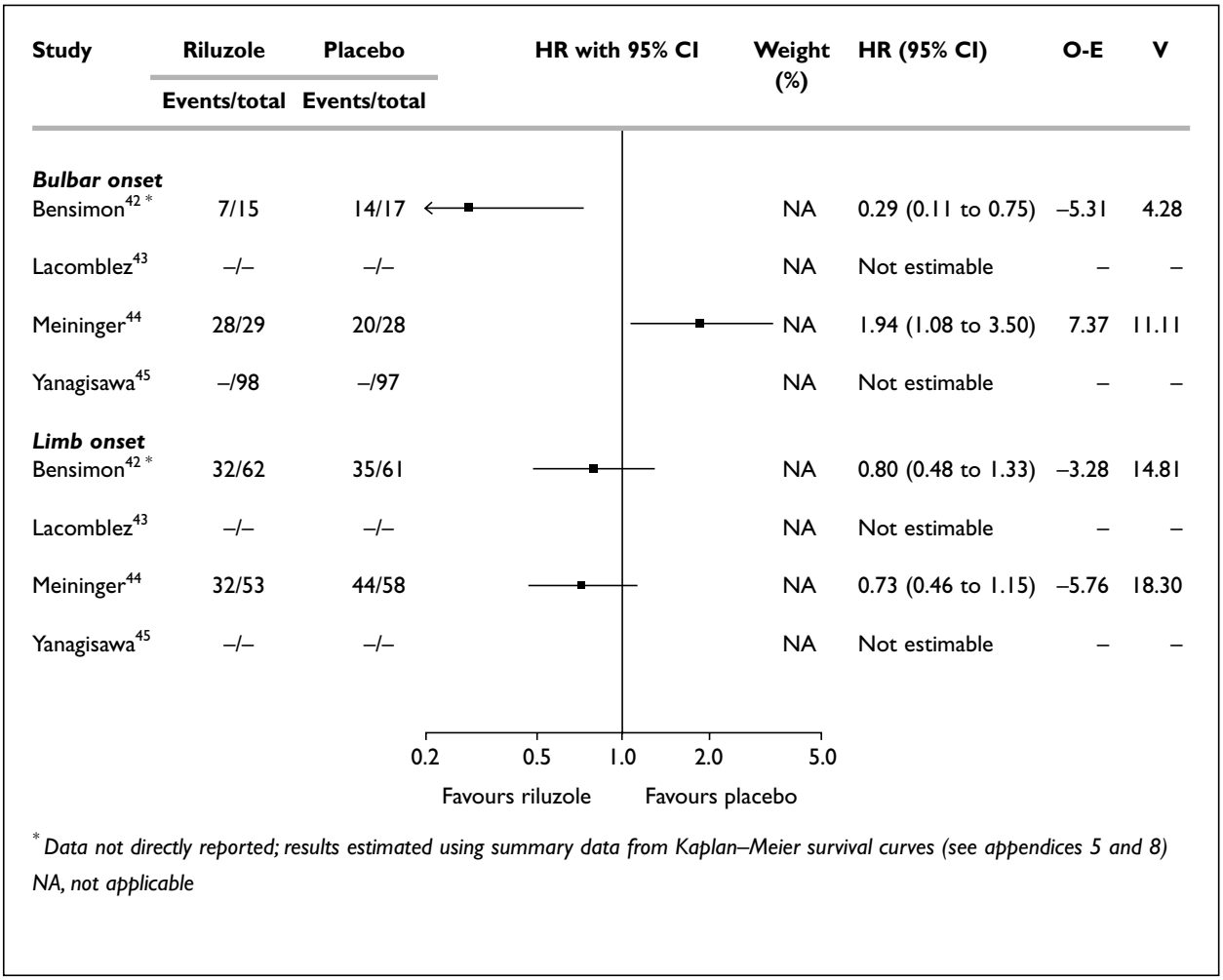
The results for progression-free survival reported by Yanagisawa and colleagues[45] do not indicate any interaction, although this trial, like Bensimon and Meininger, was small.

No formal subgroup analysis of the pooled data was undertaken because no within-group estimates were available from the largest trial (Lacomblez and co-workers[43]), which contributed about 60% of the data. Where comparisons were reported separately for the two groups, these data are summarised in *Figure 3*. Results for tracheostomy-free survival in the Yanagisawa trial are not reported for all groups and thus are not included in the figure; progression-free survival data from this trial are summarised separately in *Figure 4*.

There are clearly some differences between these trials in the results of subgroup analyses by site of onset. Two trials, including the largest, report no evidence of an interaction, whilst the other two trials (Bensimon and Meininger) both report a possible interaction but disagree as to the direction of the interaction. Subgroup analysis, particularly with trials as small as these, is notoriously unreliable. It is difficult to draw firm conclusions from the data available but, on the basis of what has been reported, there is no clear evidence of any interaction between treatment and site of onset.

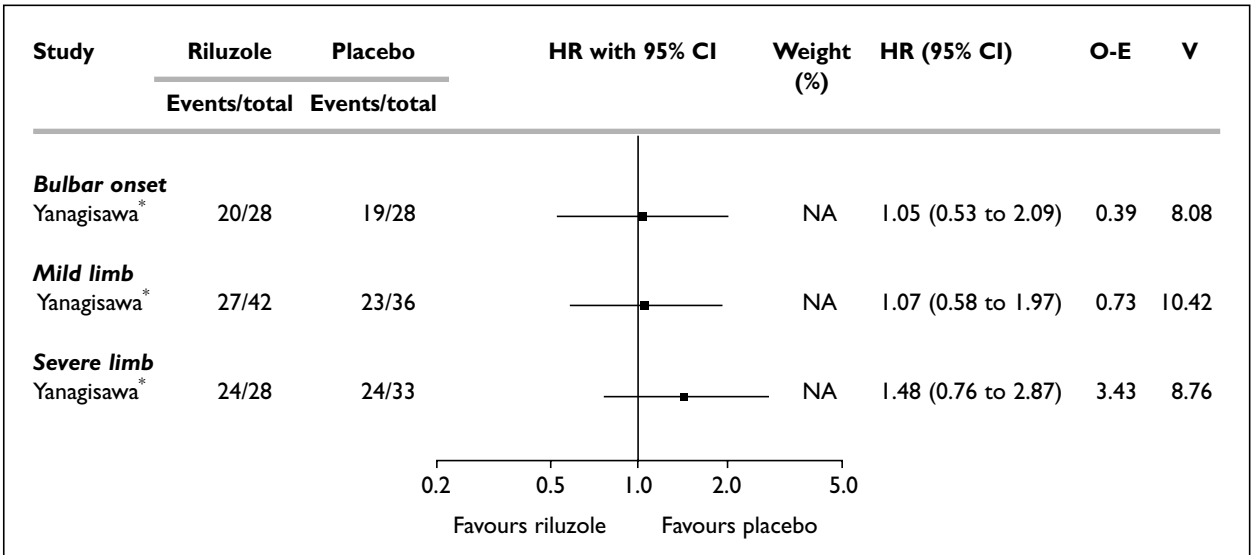
Treatment effect in subgroups – effect by 'high' and 'low' risk

Lacomblez and colleagues[43] derived a prognostic index using the Cox model and used this to divide patients into two equal groups according to risk (above and below the median risk score). The later Yanagisawa paper repeated this analysis; they updated the prognostic index derived by Lacomblez by combining their data with that of Lacomblez and Bensimon (although some patients appear to have been excluded) and then split their patients into two groups according to whether they scored above or below the median risk score for the whole data set combined. This led to only about one-third (rather than half)



* *Data not directly reported; results estimated using summary data from Kaplan–Meier survival curves (see appendices 5 and 8)*
NA, not applicable

FIGURE 3 *Treatment effect by site of onset – tracheostomy-free survival*



* *Data not directly reported; results estimated using summary data from Kaplan–Meier survival curves (see appendices 5 and 8)*

FIGURE 4 *Treatment effect by site of onset – progression-free survival (Yanagisawa and colleagues[45])*

of the Yanagisawa patients being defined as 'high' risk, which might be expected from the difference in eligibility criteria because the Japanese trial required an event-free life expectancy of at least 6 months.

Yanagisawa and colleagues[45] did not give details of the updated prognostic index that they derived using the combined data. If the two indices were broadly similar, this will have caused the cut-off (the median score of all patients combined) being at a slightly lower risk compared to that used by Lacomblez and co-workers,[43] but this difference would not have been great due to the much larger numbers in the Lacomblez trial. The high- and low-risk groups reported by Lacomblez and Yanagisawa appear to be quite similar in the two papers, with 40–50% of high-risk patients and 80–90% of low-risk patients still alive without tracheostomy at 12 months.

Yanagisawa and co-workers[45] also investigated differences in treatment effect according to risk. Although the methods (if any) used are not clear and the analysis did not involve the ITT population, they reported a trend in favour of riluzole in high-risk patients only. This subgroup analysis, particularly in such a small trial, should be treated with caution. However, Yanagisawa and co-workers stated their rationale for their 'by risk' analysis: "In overseas clinical studies performed for 18 months or shorter, riluzole was effective only in patients in whom primary endpoints occurred relatively frequently". Although no such analysis was detailed in the other trial reports available to us, the EMEA did request a similar analysis from Rhône-Poulenc Rorer based on combined individual patient data from the Bensimon, Lacomblez and Meininger studies. They report that,

> "An analysis separating patients in two risk levels: 'high risk' and 'low risk' was a posteriori performed [at the request of the EMEA], based on an initial risk index calculated for each patient. Efficacy on survival was only apparent in 'high-risk' patients of studies 216 and 301 [Bensimon and Lacomblez], thus evidencing that a benefit on survival can only be demonstrated in patients having reached a certain degree of severity of the disease."

(Note that the final part of this statement is not strictly correct, unless it is assumed that risk here is defined entirely by the stage of advancement reached, and is not related to the underlying rate of disease progression. This is inconsistent with the results of the Cox models reported from these trials. These indicate that, 'all else being equal', a longer prior duration of disease is suggestive of a better future prognosis, suggesting that underlying rate of disease progression may be an important factor in determining risk.)

Unfortunately, no further (numerical) information is available to us about the analysis performed for the EMEA or the statistical methods used, and this possible interaction needs to be investigated further before any conclusions can be drawn. Careful analysis is required because apparent interactions may easily appear by chance. Furthermore, the effect may be an artefact of the period of follow-up, as pointed out by Yanagisawa and colleagues.[45] All of these trials had very short follow-up periods (about 18 months) and, therefore, few events will have been observed in the low-risk populations; 'lack of an effect' could simply mean 'lack of power to detect an effect'. We cannot comment further without access to the data and/or more information about the methods used to examine the interaction.

Functional status

- Data on the annual rate of deterioration in muscle testing scores, limb and bulbar function were available from three of the four trials (1282 patients of a total of 1477).
- A small reduction in the annual rate of deterioration of functional status was observed; differences were marginally statistically significant for limb and bulbar function scales. It is not clear whether the observed differences were clinically significant.

Definition of endpoints

All of the trials evaluated annual rates of deterioration in muscle strength, limb and bulbar function. Lacomblez used a modified Norris scale for limb and bulbar function, with muscle strength assessed using the 'scale of the Medical Research Council'.[41] Bensimon, Meininger and Yanagisawa appear to have used the same instruments, although the scale for muscle testing was not described by these authors. Yanagisawa and co-workers[45] used the Japanese versions of the Norris scales for limb and bulbar function.

Data available

Bensimon, Lacomblez and Meininger reported mean annual rate of deterioration, with estimates of the SEM. Results for these trials individually and combined are summarised in *Table 6*. Yanagisawa and co-workers[45] analysed percentage change from baseline, but did not report the results in detail.

TABLE 6 *Summary of functional status; data are annual rates of deterioration. (Data in bold text are reported directly in the trial reports; data in roman text have been derived from information given in the trial reports. Combined results are summarised in the far right-hand column in bold italics.)*

	Bensimon et *al.*[42]			Lacomblez et *al.*[43,a]			Meininger et *al.*[44]			Combined Difference
	Placebo	Riluzole	Difference	Placebo	Riluzole	Difference	Placebo	Riluzole	Difference	
Muscle testing score (minimum score = 0, maximum score = 110)										
n	75	75		Not stated	Not stated		68	64		
Results (points per year)										
Mean	**34.40**	**22.90**	**11.50**	24.30	23.83	0.47	**28.60**	**24.20**	4.40	***2.08***
SEM	–	–	**5.20**	1.70	0.96	1.95	**3.80**	**4.20**	5.66	***1.74***
95% CI	NA	NA	1.31, 21.69	NA	NA	–3.35, 4.30	NA	NA	–6.70, 15.50	***–1.33, 5.49***
p-value			**0.028**			0.81			**0.37**	***0.23***
Bulbar score (minimum score = 0, maximum score = 39)										
n	75	75		Not stated	Not stated		68	64		
Results (points per year)										
Mean	**12.30**	**9.80**	**2.50**	11.00	9.77	1.23	**10.50**	**6.10**	4.40	***1.73***
SEM	–	–	**3.00**	0.8	0.44	0.91	**1.80**	**1.40**	2.28	***0.82***
95% CI	NA	NA	–3.38, 8.38	NA	NA	–0.56, 3.02	NA	NA	–0.07, 8.87	***0.13, 3.33***
p-value			**0.42**			0.18			**0.05**	***0.03***
Limb score (minimum score = 0, maximum score = 63)										
n	75	75		Not stated	Not stated		68	64		
Results (points per year)										
Mean	**28.10**	**21.80**	**6.30**	24.00	21.57	2.43	**16.90**	**14.60**	2.30	***2.73***
SEM	–	–	**5.20**	1.50	0.83	1.71	**2.80**	**2.90**	4.03	***1.51***
95% CI	NA	NA	–3.89, 16.49	NA	NA	–0.94, 5.79	NA	NA	–5.60, 10.20	***–0.22, 5.69***
p-value			**0.22**			0.16			**0.40**	***0.07***

[a] *All doses combined; means and SEMs estimated from plot (data not otherwise reported)*

Results (functional status)

No numerical data on functional status is available from Yanagisawa and co-workers,[45] they say only that, "there were no significant differences between the treatment groups concerning secondary endpoints based on percentages of changes in function test scores from baseline". The combined data from the other three trials do suggest a small reduction in the rate of deterioration in functional outcomes. On the basis of the information available to us, it is impossible to say what effect the addition of the results from Yanagisawa and co-workers[45] might have on this analysis.

The estimated reduction in the annual rate of deterioration is approximately 2 points for each scale, although the annual rates of deterioration in each scale range from about 30 points (muscle testing) to about 10 points (bulbar score). The relative reduction in rate of deterioration is about 10–20% for each scale, although the CIs are wide and thus consistent with much smaller or larger benefits.

It is not clear whether these differences are clinically significant. It is difficult to assess the meaning of a 2-point reduction in the annual rate of deterioration on any of these scales, and indeed whether this 2-point difference has the same meaning for a patient with a high initial score compared to one whose score is very low initially. There is no information given as to the relationship between rate of deterioration and initial score, or whether the absolute reduction was broadly similar for patients with high and low initial scores. More complex methods of analysis, such as analysis of covariance or longitudinal methods, would be more appropriate for this type of data. It is not possible for us to consider these data in more detail without access to the individual patient data.

An important point to note is that estimated differences in rates of change of functional status may be biased, given differences in survival between the two treatment groups. When there are observed differences in survival, longitudinal data collected from the survivors in each group are not strictly comparable, because there are a small number of patients who are 'alive and contributing data' on one arm whose counterparts in the other treatment group arm are 'dead and not contributing data'. The effect of this 'informative censoring' may mask true effects, or give rise to spurious ones; assigning a 'zero' rate of deterioration to patients who have died would not be an adequate means of addressing the problem. Methods are available to adjust longitudinal measurements for survival differences, but these cannot be applied to the summary data available to us. Note that these three trials present the data as annual rates of deterioration. No information is given as to intra-patient changes in rates of deterioration over time in each of these scales, which may be increasing, decreasing or constant. The likely effect of informative censoring in this case is, therefore, impossible to assess.

Adverse events and safety

- A large proportion of patients reported adverse events but there was little difference in these proportions between riluzole and placebo.
- Treatment withdrawal rates in these studies varied widely, from 6% to 25% for patients taking riluzole, although two of the studies reported quite similar withdrawal rates with placebo as with riluzole.

Adverse events were roughly equal for placebo and riluzole. Trials by both Bensimon and colleagues[42] and Meininger co-workers[44] reported about twice as many withdrawals for riluzole compared to placebo, whereas both Lacomblez and colleagues[43] and Yanagisawa and colleagues[45] report similar numbers of withdrawals in each arm. The most frequently reported adverse events included respiratory disorders, dysphagia, asthenia, apnoea and nervous system disorders. Adverse events occurring more frequently in patients taking riluzole included increased alanine aminotransferase (ALAT) or aspartame aminotransferase (ASAT) asthenia, nausea and abdominal pain. A summary of adverse events is shown in *Table 7*.

The European Agency for the Evaluation of Medicinal Products reported that of approximately 5000 patients with ALS who took riluzole, three cases of neutropenia were reported. These all occurred within 2 months of riluzole treatment. No events on cognitive, cardiovascular or respiratory functions were observed.[57] They reported the number of adverse events that occurred in the trials by Bensimon and co-workers,[42] Lacomblez and colleagues[43] and Meininger and colleagues[44] at a frequency of 1% or more in ALS patients on riluzole 100 mg daily, and this was greater than with placebo by 1% or the occurrence of serious adverse events was more frequent than with placebo (see *Table 8*).

TABLE 7 *Adverse events*

	Bensimon *et al.*[42]		**Lacomblez *et al.*[43]**				**Meininger *et al.*[44]**		**Yanagisawa *et al.*[45]**	
	Placebo	**Riluzole 100 mg**	**Placebo**	**Riluzole 50 mg**	**Riluzole 100 mg**	**Riluzole 200 mg**	**Placebo**	**Riluzole 100 mg**	**Placebo**	**Riluzole 100 mg**
Those with adverse events	91%	93%	90% reported adverse events, but numbers not given for individual groups				91%	91%	18%	24%
Those with treatment withdrawn	12%	25%	21%	21%	23%	22%	7%	14%	7% (number of drop-outs for side-effects)	6%
Most frequent adverse events:									Conditions classed as mild/moderate/severe	
Respiratory system							67%	54%	1%	3%
Respiratory disorders	43%	39%								
Bronchitis			18%	17%	15%	14%				
Lung function decrease			13%	13%	14%	16%				
Asthenia	15%	26%	13%	15%	18%	20%				
Dysphagia	11%	8%	20%	18%	20%	17%				
Nausea			13%	13%	21%	21%				
Apnoea			12%	10%	11%	8%				
Increased ALAT/ASAT	8%	17%								
Headache (including dull headache)									11%	8%
Muscle spasm/ rigidity									5%	4%
Body as a whole							64%	52%		
Digestive system							19%	15%		
Cardiovascular system							8%	17%		
Nervous system							4%	7%		
Others									5%	8%
General									3%	6%

TABLE 8 *Adverse events occurring more frequently in riluzole than placebo*

	Adverse events occurring in placebo-controlled clinical trials Percentage of patients reporting events[a]	
	Riluzole 100 mg daily (*n* = 395)	**Placebo (*n* = 406)**
Asthenia	17.5	11.3
Nausea	14.2	9.1
Headache	6.8	5.7
Abdominal pain	5.1	3.7
Pain	4.8	2.0
Vomiting	3.8	1.5
Dizziness	3.3	2.2
Tachycardia	3.0	1.5
Somnolence	2.0	1.0
Circumoral parasthesia	1.3	0.0

[a] *Where riluzole incidence is greater than placebo by 1%*

Chapter 4

Results – health economics

Drug cost

The recommended dose is 50 mg twice daily (i.e. 100 mg daily). Riluzole costs £286.00 for 56 × 50 mg tablets,[30] which equates to about £3700 per year. It should be noted that existing evidence does not indicate that this dose is any more beneficial than 25 mg twice daily (see appendix 9).

Existing economic evaluations

- Eight economic studies were found
- Base-case incremental cost-effectiveness ratio (ICER) is highly variable, with up to a five-fold variation, the most optimistic being the Tavakoli/Aventis model
- The key parameter driving the variation is the gain in life-years
- The key assumption in estimating the gain in life expectancy concerns the extrapolation beyond observed survival
- All cost analyses were hampered by the fact that resource-use data were not collected in clinical trials.

Studies found

A total of eight economic studies were identified.[21,31,54,59–63] Four were original economic evaluations of riluzole published in peer-reviewed journals,[60–63] two were systematic reviews that included some consideration of economic issues,[31,54] one was a review of an unpublished report[59] and one was the economic analysis reported in the Aventis submission to NICE.[21] A confidential unpublished report undertaken by the Benefit Research Group was obtained by the review team, but we were unable to get a response from the group in order to gain approval to quote from it. The focus for this section of the report is on the original analyses reported in peer-reviewed journals and the new data reported in the Aventis NICE submission.

Study characteristics and results

Table 9 details some of the key study characteristics and reports the results for the base-case cost-effectiveness analyses (CEAs). All studies compared treatment with riluzole against service provision without riluzole, either 'standard therapy' or 'best supportive care'. The study described by Gray[60] was the only one to consider the cost-effectiveness of different dosages of riluzole. In the published literature, all studies used a CEA framework, reporting the incremental costs per additional life-year for riluzole treatment. The only study that adopted a cost–utility analysis (CUA) approach is the Aventis NICE submission. (However, according to the published review of the report by the Benefit Research Group, the Benefits Research Group also performed a CUA study.[13])

As shown in *Table 9*, the base-case results relating to survival and costs reveal marked disparities between studies. Only three studies (Gray,[60] Ginsberg and Lev[61] and Messori and co-workers[62]) report these parameters – the study by Tavakoli and co-workers[63] and the Aventis submission[21] only provided the base-case ICER and did not report base-case parameters for costs and survival separately. Unsurprisingly, the base-case ICERs also varied widely between the studies.

In an attempt to understand why the studies have come to such different conclusions regarding the cost-effectiveness of riluzole, the data and assumptions used in constructing the base-case analyses were explored (*Table 10*) and the sensitivity analyses undertaken were reviewed (*Table 11*). The results of these analyses are reported in the following four sections.

Analysis of survival data

Survival data for two of the economic analyses (Gray[60] and Messori and colleagues[62]) were drawn from two of the published trials (Bensimon and co-workers[42] and Lacomblez and co-workers[43]). Given that the analysis by Gray considered the cost-effectiveness of alternative dosages, survival data for each dose were analysed separately. Messori and co-workers used data for patients in the 100 mg riluzole trial arm only. The analysis reported by Tavakoli and colleagues[63] and the Aventis NICE submission[21] used data from only a single trial (Lacomblez and colleagues[43]) and included data for all riluzole arms; the cost-effectiveness of dosages other than 100 mg was not explored. Ginsberg and Lev[61] did

TABLE 9 *Assessment of published CEAs of riluzole: study characteristics and results*

Criterion	Gray, 1998[60]	Ginsberg and Lev, 1999[61]	Messori *et al.*, 1999[62]	Tavakoli *et al.*, 1999[63]	Aventis NICE submission[21]
Comparators	Riluzole treatment (100 or 50 mg) versus placebo	Riluzole treatment (100 mg) versus care without riluzole	Standard supportive therapy plus riluzole (100 mg) versus standard supportive therapy without riluzole	Riluzole treatment (100 mg) versus best supportive care (as proxied by placebo group in trial)	Riluzole treatment (100 mg) versus best supportive care (as proxied by placebo group in trial)
Perspective	Health sector	Health sector and society	Health sector	Health sector	Health sector
Type of economic evaluation	CEA[a]	CEA[a] and CBA[b]	CEA[a]	CEA[a]	CUA[c]
Base-case survival result	Life-years gained: 50 mg 0.041 100 mg 0.089	Assumptions: 3-year life expectancy for patients with ALS which is extended by 3 months using riluzole	Mean lifetime survival (discounted months): riluzole 19.7 standard therapy 17.4	Not stated (but estimated survival curves displayed)	Not stated
Base-case cost result: incremental costs of riluzole	Riluzole 50 mg = £1,860 Riluzole 50 mg = £3,984	Health sector costs only: $US 757 Health sector costs plus productivity savings: – $US 2,884	$US 11,966	Not stated	Not stated
Base-case ICER	Riluzole 50 mg = £45,630 per life-year gained Riluzole 100 mg = £44,890 per life-year gained	Health sector costs only: $US 12,013 per life-year gained Societal perspective: Dominance (i.e. negative costs, positive benefits)	$US 62,609 per life-year gained	£8,587 per life-year gained	£12,384 per QALY gained
Funding/ sponsorship	None acknowledged	Israeli Ministry of Health	None acknowledged	Rhône-Poulenc Rorer	Aventis

[a] *Incremental cost per life-year gained*
[b] *CBA, cost–benefit analysis*
[c] *Incremental cost per QALY gained*

not state the source of their survival estimates. All five reports analysed the survival data very differently for the economic evaluations. The key parameters that require estimation are mean life expectancy with riluzole and mean life expectancy without riluzole. Whilst such data provide an indication of the incremental gain in survival, they are also necessary for the cost-analysis since the assumption is generally made that riluzole will be taken until the patient's death. In all trials, patients on placebo were switched to riluzole at the end of follow-up and thus no longer-term survival data for placebo patients is available. The implication of this is that extrapolation beyond the follow-up data observed in the trials is required (i.e. extrapolating from observed survival to predicted life expectancy). Gray[60] did not extrapolate beyond the trial end, and Ginsberg and Lev[61] made no reference to the issue of survival extrapolation.

TABLE 10 *Assessment of published CEAs of riluzole: effectiveness and cost data*

Criterion	Gray, 1998[60]	Ginsberg and Lev, 1999[61]	Messori *et al.*, 1999[62]	Tavakoli *et al.*, 1999[63]	Aventis NICE submission[21]
Source(s) for survival data	Bensimon and colleagues and Lacomblez and colleagues (for riluzole group, patients treated with either 50 or 100 mg)	Not stated/ assumption	Bensimon and colleagues and Lacomblez and colleagues (for riluzole group, only patients treated with 100 mg)	Lacomblez and colleagues (for riluzole group, data from all patients regardless of dose)	Lacomblez and colleagues (for riluzole group, data from all patients regardless of dose)
Analysis of survival data	Survival months lost and life-years gained No extrapolation beyond trial end	Not stated	Pooled survival analysis (log-rank and Cox) Extrapolation to lifetime survival through Gompertz analysis	Markov model based on (a) observed trial data and (b) extension of the 18-month transition probabilities for both groups 'using linear interpolation between successive probabilities'	Markov model based on (a) observed trial data and (b) extension of the 18-month transition probabilities for both groups 'using linear interpolation between successive probabilities'
Quality-of-life data	Not considered	Not considered	Not considered	Not considered	SG and EQ-5D VAS
Resource use data	Drug costs and tracheostomy costs only	Costs (savings) associated with hospitalisations, serum ALAT testing, operation costs, drug costs and other medical costs	Drug costs and patient monitoring only	Costs of care for patients with ALS health states, drug costs and patient monitoring	Costs of care for patients with ALS health states, drug costs and patient monitoring
Source(s) for cost data	Published or routine sources	Published or routine sources	Published sources	Costs of care for patients with ALS health states from Munsat and co-workers[65] Other costs from routine sources	Costs of care for patients with ALS health states from Munsat and co-workers[65] Other costs from routine sources
Analysis of cost data	Simple calculation	Simple calculation	Simple calculation	Simple calculation	Simple calculation
Price year	1997	1996	1996	1996	1999
Discounting	No discounting	Costs and benefits discounted at 5%	Both life-years and costs discounted at 3%	Life-years not discounted Costs discounted at 6%	Life-years not discounted Costs discounted at 6%

SG, standard gamble

EQ-5D, EuroQoL quality-of-life measurement instrument

VAS, visual analogue scale

TABLE 11 *Assessment of published CEAs of riluzole: sensitivity analyses*

Criterion	Gray, 1998[60]	Ginsberg and Lev, 1999[61]	Messori *et al.*, 1999[62]	Tavakoli *et al.*, 1999[63]	Aventis NICE submission[21]
Approach	1-way	1-way	1-way	1-way	1-way
Parameters	Quality-of-life adjustment (simple assumptions) Cost of tracheostomy (simple assumption)	Survival with ALS without riluzole (18–24 months) Riluzole-induced extension to life expectancy (1–5 months)	Survival gain (lower and upper 95% CIs) Drug price (substituted USA price for UK or Italian price) Other health service cost per patient (estimate used by Ginsberg and Lev)	Costs of each health state experienced by patients with ALS	Benefits discounted SG/VAS utility scores Health states
Results	Results sensitive to quality-of-life assumptions	Results highly sensitive to variation in survival gain	ICER highly sensitive to variation in survival gain	Results not highly sensitive to variation in the cost of care	Results not highly sensitive to variation in any of these parameters

Messori and colleagues[62] applied a Gompertz model to the survival curves (*Figure 5*) that allowed them to be extrapolated and mean lifetime survival to be estimated (as area under the survival curve). The base-case analysis reported a difference in mean lifetime survival between trial arms of 2.4 months (undiscounted). The Gompertz model represents one possible approach to extrapolation and the authors did not justify their choice of this approach. It would have been useful if, as part of their sensitivity analysis, the authors had explored the robustness of the results to alter-native models,

Please see the original paper by Messori and colleagues[62] (Messori A, Trippoli S, Becagli P, Zaccara G on behalf of the Italian Cooperative Group for the Study of Meta-Analysis and the Osservatorio SIFO sui Farmaci. Cost effectiveness of riluzole in amyotrophic lateral sclerosis. *Pharmacoeconomics* 1999;**16**:153–63), as permission to reproduce this figure has not been obtained.

FIGURE 5 *Gompertz extrapolation of survival – Messori and colleagues*[62]

such as Weibull or exponential. (Note that this is done in our analysis reported later in this section of the report.)

Tavakoli and colleagues[63] (and the Aventis NICE submission[21]) adopted an alternative approach: the Markov model. Using data from the Lacomblez and co-workers[43] trial and the re-analysis of the data reported by Riviere and colleagues,[46] a Markov model was constructed to estimate survival from the point of entry into the trial through to death for all trial patients. The authors indicate that they used transition probabilities that were allowed to 'vary by time', although no indication is given on how this was achieved. The paper reports observed survival (in the trial) and predicted survival (using the Markov model) through the presentation of survival curves (*Figure 6*). The authors suggest that, "for the first 18 months of the trial data, both arms of the Markov model follow the Kaplan–Meier curve accurately". The predicted survival curves do not fit the trial data perfectly – the divergence between the predicted survival curves for riluzole and placebo is most prominent after 18 months, for which no unconfounded comparative observed data exist. Between 18 and 36 months, the predicted survival curve for riluzole is consistently above the observed survival for the riluzole cohort from the trial. The authors explain the process of estimation beyond 18 months as follows:

> "in order to assess the long-term effects of riluzole on survival, the 18-month transition probabilities for both cohorts (riluzole and best supportive care) were extended using linear interpolation between successive probabilities, and the process was ended when over 99% of patients from the cohort entered the dead state."

It is not clear what this statement means. The estimated difference in mean lifetime survival between the riluzole and placebo groups appears to be about 12 months in this analysis. (Note that this survival gain is not reported in the paper – the estimate is derived from visual inspection of two figures in the paper by Tavakoli and co-workers.[63]) Our general conclusion on the survival analysis reported in this paper (and the Aventis NICE submission[21]) is one of caution. There is not enough information to allow a judgement on whether or not the Markov model has been used appropriately, and the estimate of lifetime survival gain is very different from that reported by Messori and colleagues (and that reported later in this report).

Please see the original paper by Tavakoli and colleagues[63] (Tavakoli M, Davies HTO, Malek M. Modelling the long-term cost-effectiveness of riluzole for the treatment of amyotrophic lateral sclerosis. *J Drug Assessment* 1999;**2**:219–32), as permission to reproduce this figure has not been obtained. The extrapolated survival curves are also shown in *Figure 17* (page 79).

FIGURE 6 *Observed and predicted survival – Tavakoli and colleagues[63]*

Update: the Markov model used by Tavakoli and co-workers[63] and employed in the Aventis submission was provided by the company after this review was completed. The model is reviewed in more detail in the update section at the end of the report.

CUA

The only available CUA is that reported in the Aventis NICE submission.[21] Utility scores for four ALS health states were collected from a small sample of patients with ALS in each of the four states (n = 15, 21, 21 and 19 for states I to IV, respectively). The health states used are those defined by Riviere and colleagues[46] (*Table 12*). Elicitation of utility scores was undertaken using direct standard gamble (SG) questions and indirectly using the EuroQol quality-of-life measurement instrument (EQ-5D). The reported scores for EQ-5D were those obtained using the visual analogue scale (VAS) component of the instrument – these do not represent health state utilities since the VAS is anchored by 'best imaginable health state' and 'worst imaginable health state' and not 'full health' and 'death' as required for adjustment of life-years in constructing estimates of quality-adjusted life-years (QALYs). It is surprising that utilities for EQ-5D data were not reported using the University of York Measurement and Valuation of Health Tariff.[65] It is not stated in the report whether the SG or EQ-5D VAS scores were used in the CUA.

Update: the Markov model used by Tavakoli and co-workers[63] and employed in the Aventis submission was provided by the company after this review was completed. The model is reviewed in more detail in the update section at the end of the report.

Cost data

For the cost analyses, all evaluations were hampered by the fact that data on resource use were not collected within the clinical trials. Therefore, all cost-analyses are relatively simple, although that conducted by Tavakoli and co-workers[63] draws upon published UK unit costs for ALS health states reported by Munsat and co-workers.[65] However, the estimates of time in each health state were derived from the Markov model and should thus be viewed with some caution given the earlier discussion. Only one study (Ginsberg and Lev[61]) considered a broader perspective; they included financial estimates of productivity losses and gains. In estimating lifetime drug costs, the study by Messori and colleagues was the only one to appropriately make an adjustment to reflect the observed patient withdrawal from the riluzole treatment arms in the trials. In total, 25% of riluzole patients withdrew from treatment in both the Lacomblez and Bensimon trials.[42,43]

Sensitivity analysis

None of the studies conducted an extensive sensitivity analysis (*Table 11*). From the analyses conducted, the unsurprising finding is that the cost-effectiveness results are highly sensitive to variation in the estimate of survival gain.

Economic evaluation

- A model was developed to explore the uncertainties identified in previous analyses, from a health service perspective
- Survival data were taken from combined results of trials by Lacomblez and colleagues[43] (all riluzole doses) and Bensimon and

TABLE 12 *ALS health states*[46]

State I (Mild) Recently diagnosed Mild deficit only in one of the three regions (speech, arm, leg) Functionally independent in speech, upper extremity, activities of daily living and ambulation
State II (Moderate) Mild deficit in all three regions Moderate to severe deficit in one region while the other two regions are normal or mildly affected
State III (Severe) Needs assistance in two or three regions Speech is dysarythric and/or patient needs assistance to walk and/or needs assistance with upper extremity functions and activities of daily living
State IV (Terminal) Non-functional use of at least two regions and/or moderate or non-functional use of the third region

colleagues[42] using an optimistic assumption in favour of the drug
- Extrapolation beyond observed survival was undertaken using a Weibull model
- Base-case ICER gave a cost per life-year of £39,000 and a cost per QALY of £58,000
- A sensitivity analysis indicated that the most optimistic ICER (cost per QALY) is £20,000 and the most pessimistic has riluzole dominated by placebo.

Base-case values and parameters

The parameters used in the base-case economic analysis undertaken for this review are reported in *Table 13*. Where possible, the economic analysis used trial data or data from other published sources. The implication of using trial data in the base-case analysis is that the population of patients with ALS being considered is the same as that seen in the trials, which were dominated by prevalent (rather than incident) cases of ALS. The importance of this assumption is explored in the sensitivity analysis.

The survival estimates have been taken from the meta-analysis reported earlier in this report using data from the Bensimon and Lacomblez (all riluzole dosages combined) trials only – the Meininger trial was excluded to avoided further heterogeneity in the patient group. Extrapolation beyond the observed survival in the trials has been undertaken using a Weibull model,[66] and the survival curves resulting from this analysis are shown in *Figure 7*. The mean survival for patients in each group was estimated as the area under the survival curve. On the basis of the re-analysis of trial data reported by Riviere and colleagues,[46] on time spent in each ALS health state, an assumption in the base-case analysis has been that the increase in survival brought about by riluzole is experienced in ALS health state II.

The economic analysis adopted a health service perspective and thus considered costs incurred within the health sector only. These included costs associated with the drug itself, the associated serum ALAT testing and the general costs of caring for patients with ALS over the extended survival period. For the base-case, all future costs and benefits were discounted at a rate of 6%. In the trials, it was observed that 25% of patients who began on riluzole withdrew from the treatment, and the cost-analysis assumed that such a withdrawal rate would be seen in routine practice and cost-estimates were adjusted accordingly. The economic evaluation includes both CEA (cost per life-year gained) and CUA (cost per QALY gained), both using an incremental approach with a focus on the increase in both the costs and the effectiveness. Data on quality of life were taken from the SG utility estimates reported in the Aventis NICE submission.[21]

TABLE 13 *Base-case parameters for the economic analysis (Price base: 1999)*

Parameters	Value	Source
Undiscounted survival (months) with riluzole	21.38	Current review (Weibull extrapolation)
Undiscounted survival (months) with placebo	19.67	Current review (Weibull extrapolation)
Discounted survival (months) with riluzole	20.85	Current review (Weibull extrapolation)
Discounted survival (months) with placebo	19.24	Current review (Weibull extrapolation)
Proportion of patient withdrawals from riluzole	0.25	Bensimon *et al.*[42] and Lacomblez *et al.*[43] trials
Riluzole cost per daily dose (£)	10.21	£286 per 56 x 50 mg tablets
Patient monitoring cost per month (£)	17	Tavakoli *et al.*[63]
Annual care cost – ALS health state I	1236.61	Munsat *et al.*[65]
Annual care cost – ALS health state II	834.28	Munsat *et al.*[65]
Annual care cost – ALS health state III	1771.42	Munsat *et al.*[65]
Annual care cost – ALS health state IV	3263.17	Munsat *et al.*[65]
Discount rate	6%	UK Treasury
Utility – ALS health state I	0.79	Aventis NICE submission[21]
Utility – ALS health state II	0.67	Aventis NICE submission[21]
Utility – ALS health state III	0.71	Aventis NICE submission[21]
Utility – ALS health state IV	0.45	Aventis NICE submission[21]

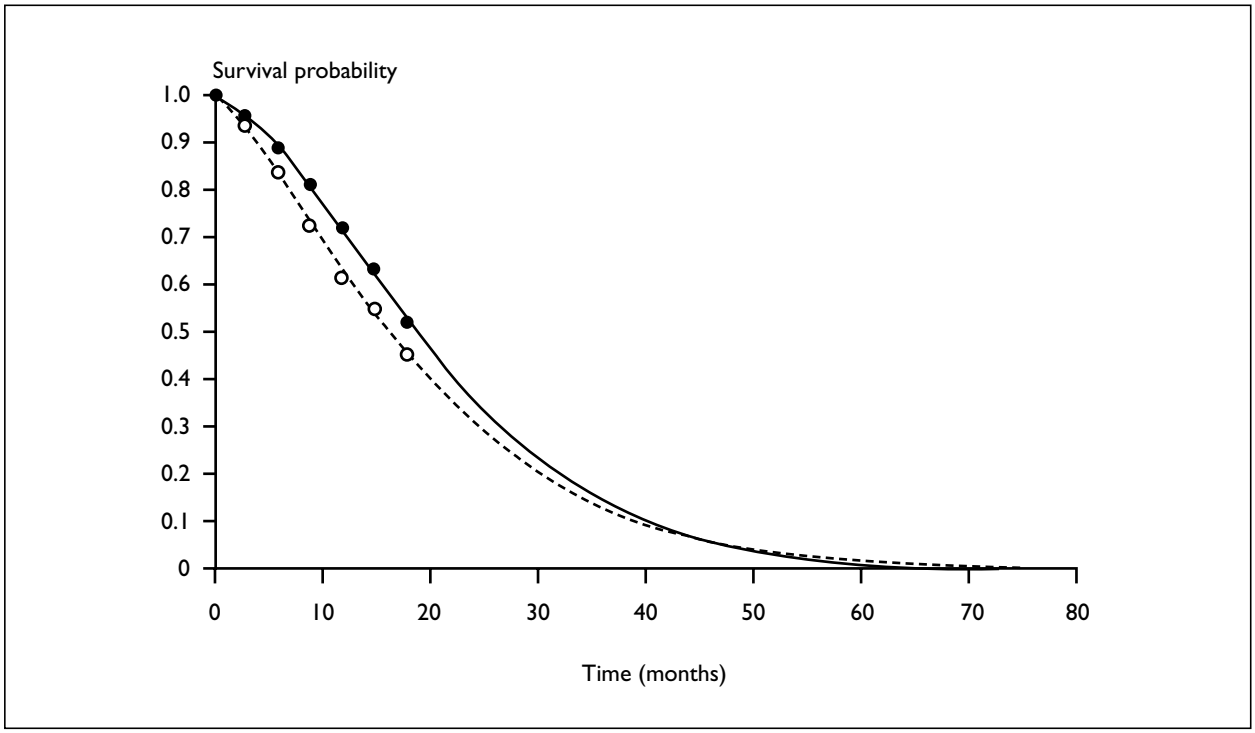


FIGURE 7 *Survival curves with Weibull extrapolation (——, riluzole: Weibull; – – –, placebo: Weibull; ●, riluzole: observed; ○, placebo: observed)*

Base-case results

The results of the base-case economic analysis are reported in *Table 14*. The results indicate that riluzole is associated with an increase in expected lifetime survival of 0.13 years which translates into 0.09 QALYs on the assumption that the gain is experienced in ALS health state II. The expected additional discounted cost to the health service is £5200 per patient over the remainder of the patient's life.

Sensitivity analysis

The robustness of the base-case results was explored through the use of sensitivity analysis. *Table 15* provides an indication of the parameters that were varied. First, the importance of using the trial population with predominantly prevalent cases of ALS was explored. The assumption was made that all patients to receive riluzole would be incident cases and so the life expectancy of patients would be longer by about 2 years. This has implications for the total cost since riluzole is now being taken for a longer period and may have implications for benefits. However, there is currently no evidence upon which to base such an assertion. Therefore, two separate assumptions concerning survival gain were made independently: (1) the absolute increase in life-years for the incident population is the same as that seen in the trials; and (2) the absolute gain in life-years is greater for incident patients by the same proportion as the increase in the duration of therapy.

TABLE 14 *Base-case results for economic analysis*

Results	Value
Lifetime cost of riluzole	£4,841
Lifetime cost of monitoring	£242
Additional care costs due to survival increase	£112
Life-years gained	0.13
QALYs gained	0.09
Increase in costs	£5,200
ICER (cost per life-year)	£39,000
ICER (cost per QALY)	£58,000

As indicated in the review of existing economic studies, the estimate of lifetime survival gain is a key driver of the results of the economic analysis. This suggests that the process of extrapolation beyond observed survival requires careful consideration. The Markov model used by Tavakoli and colleagues[63] (and the Aventis NICE submission[21]) resulted in a predicted survival gain of approximately 12 months. This is very different to the predicted survival gain of 2–3 months by Ginsberg and Lev[61] and Messori and colleagues.[62]

TABLE 15 *Sensitivity analysis results*

Parameter	Gain in life-years	Gain in QALYs	Increase in cost (£)	ICER (cost per life-year)	ICER (cost per QALY)
Base-case result	0.13	0.09	5,200	39,000	58,000
Riluzole given to incident population (i.e. assuming that patients start taking riluzole 2 years earlier, on average, than trial patients):					
– Assuming the same absolute gain in life-years as in the base-case	0.13	0.09	9,700	72,000	107,000
– Assuming that the absolute gain in life-years is greater by the same proportion as the increase in duration of therapy	0.27	0.18	10,700	39,000	58,000
Variation in survival estimates:					
– Using a Gompertz model for survival extrapolation for both placebo and riluzole	0.08	0.05	4,500	59,000	88,000
– Using a Gompertz model for placebo and Weibull model for riluzole extrapolation	0.31	0.21	5,300	17,000	25,000
– Using a Weibull model for placebo and Gompertz model for riluzole extrapolation	–0.10	–0.07	4,300	–42,000[a]	–62,000[a]
– Assuming 1 month survival gain for riluzole (as an estimate of the upper 95% CI limit)	0.08	0.05	5,000	66,000	98,000
Variation in health state assumption:					
– Survival gain distributed evenly across all four ALS health states	0.13	0.09	5,300	40,000	60,000
– All survival gain experienced in health state IV	0.13	0.06	5,500	41,000	91,000
Discount rate:					
– Benefits undiscounted, costs discounted at 6%	0.14	0.10	5,200	37,000	54,000
– Costs and benefits discounted at 3%	0.14	0.09	5,200	38,000	56,000
Variation in dose of riluzole:					
– 50 mg per day	0.13	0.09	2,800	21,000	31,000

[a] *Riluzole associated with higher cost and lower survival than placebo*

In order to explore the importance of using a Weibull model for extrapolation in the base-case model, an alternative approach (a Gompertz model) was used in the sensitivity analysis to extrapolate survival for both placebo and riluzole groups, in line with Messori and colleagues (*Figure 8*). In addition, as a best-case scenario for survival gain with riluzole, the Gompertz model was used for placebo and the Weibull for riluzole; and as a worst-case survival scenario the Weibull model was used for placebo and the Gompertz model for riluzole. Estimates of survival gain in line with upper and lower 95% CI limits were also explored.

The base-case analysis assumed that the survival gain was experienced in ALS health state II. This was varied in the sensitivity analysis to consider an equal share of the gain across all four ALS health states and, as a worst-case scenario for riluzole, to consider the gain being restricted to the terminal state (state IV). In addition, variation in the daily dosage of riluzole and the discount rate were explored.

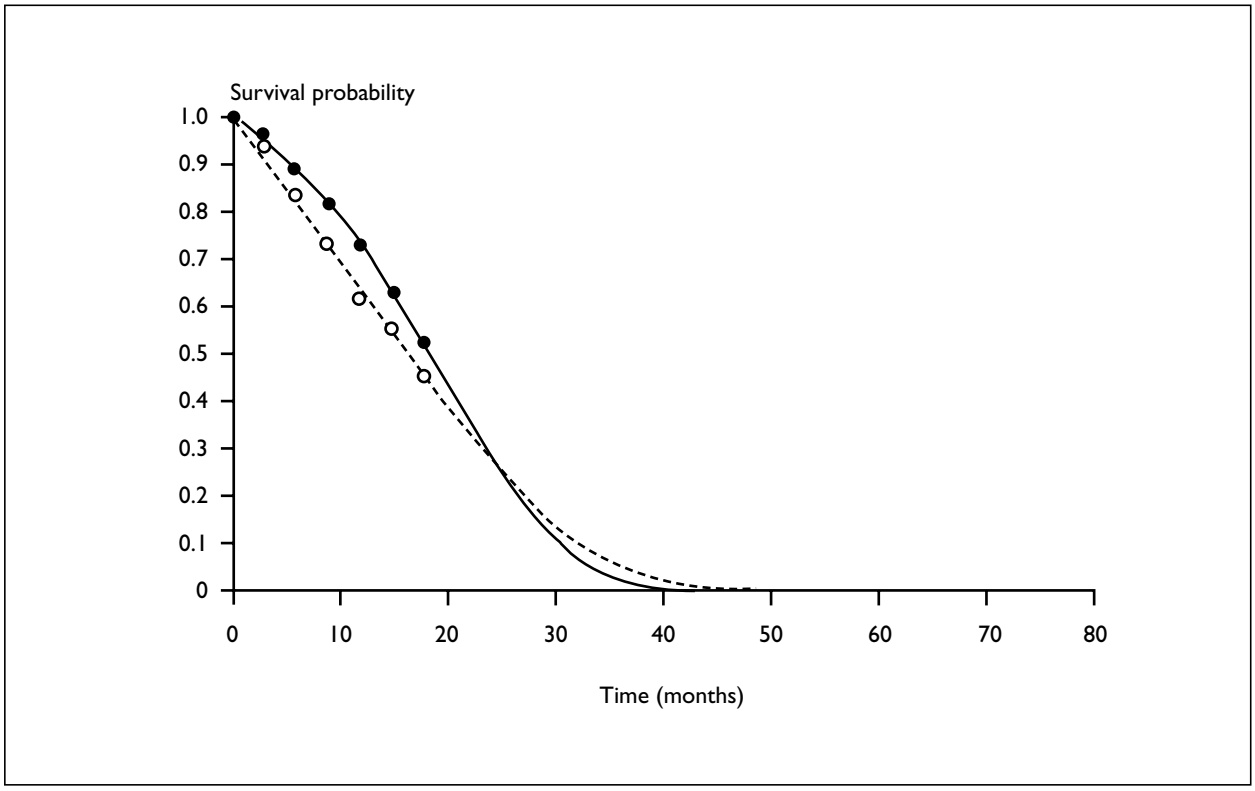


FIGURE 8 *Survival curves with Gompertz extrapolation (——, riluzole: Gompertz; – – –, placebo: Gompertz; ●, riluzole: observed; ○, placebo: observed)*

Key points from the sensitivity analysis:

- The sensitivity analysis indicates that the base-case results are reasonably robust to variation in the health state assumptions and to discount rate variation.
- The cost-effectiveness of riluzole is, unsurprisingly, more attractive when a 50 mg daily dose is used, assuming no reduction in effectiveness; there is no evidence to suggest that there is any difference in effectiveness between the two dosages (50 and 100 mg daily), although there is insufficient data to rule out the possibility of a moderate dose–outcome relationship.
- The use of riluzole in an incident population is associated with a marked increase in costs given the longer period of time over which the drug is taken. The impact of this on the ICER depends on the extent to which the gain in life-years is influenced by the earlier use of riluzole, and there are no adequate published data that address this question.
- The sensitivity analysis reiterates the finding that a key driver of the cost-effectiveness result is the survival gain associated with riluzole. The use of alternative models to extrapolate beyond observed survival provide results that vary widely. Further research is required to improve on the extrapolation process in this particular case. This might be achieved by using longer-term follow-up data for the riluzole cohorts of trial patients (all placebo patients were offered the switch to riluzole at the end of trial follow-up) and exploration of data on the natural history of ALS in the absence of riluzole.
- The plausible range is that the most optimistic ICER (cost per QALY) is £20,000 and the most pessimistic has riluzole dominated by placebo.

Limitations of the economic analysis

Survival extrapolation would be useful to:

- Construct a simulation model to explore further the robustness of the longer-term survival gain estimates
- Have access to further data on trial patients in the riluzole arms to observe survival beyond 18 months
- Explore the natural history of ALS in order to facilitate improved estimation of survival without riluzole.

It would also be useful to obtain better data on:

- The effectiveness for lower dose (50 mg daily) and for earlier use (i.e. for use in an incident population)

- The costs of caring for patients with ALS
- The quality of life/utility data – based on a larger survey of patients than obtained in the Aventis NICE submission.[21] The individual variability of the values needs to be carefully considered.

Conclusions

The evidence presented in this report suggests that current estimates of the cost-effectiveness of riluzole must be viewed cautiously given the great uncertainties relating to many of the cost and benefit parameters. On the basis of the review and analyses presented in this section of the report, it is clear that the base-case economic analysis detailed in the Aventis NICE submission[21] (and the paper by Tavakoli and colleagues[63] upon which the submission was based) is highly optimistic.

Update: the Markov model used by Tavakoli and co-workers[63] and employed in the Aventis submission was provided by the company after this review was completed. The model is reviewed in more detail in the update section at the end of the report.

The principal benefit claimed for riluzole is an increase in survival. Some of the key remaining uncertainties concerning the benefits within the economic analysis are (1) the disease stage at which the survival gain is experienced, (2) the quality of life utility weights for ALS health states and (3) the mean gain in life expectancy for patients who take riluzole. The central issue is the life expectancy gain. As indicated above, published estimates of the increase in survival range from 2 to 12 months. It is clear that riluzole is associated with a net increase in costs to the health service. However, the magnitude of the increase is difficult to predict accurately. The main reason for this is uncertainty concerning the length of the period over which the drug will be administered.

A more robust estimate of any riluzole-induced gain in life expectancy is required to reduce current uncertainties concerning the appropriate methods of extrapolating beyond observed survival. Therefore, economic analysis in this area would be greatly improved through further research to strengthen the current estimates for the survival gain parameter. In particular, the current analysis would have been strengthened had the research team been given access to the longer-term survival data (up to 50 months) for riluzole held by Aventis.

Update: some longer-term follow-up was provided by the company after this review was completed. The new data are addressed in the update section at the end of the report.

Chapter 5

Patient perspectives

- Quality of life in ALS is not determined merely by functional state.
- Some patients with ALS do not want to extend their lives.
- Some patients do not think the side-effects of riluzole are worth the benefits.
- Some patients want the hope that riluzole represents, or need to feel they are fighting back.
- The availability of riluzole does not alter the need for responsive palliative care.

ALS is amongst the most serious of diseases. Moreover, it is a disease that most people know little about. People with ALS experience a steady loss of their ability to move and function, and an erosion of their autonomy.[2] They know that they have a relentlessly progressive and fatal disease. Problems are exacerbated by the involvement of the muscles used for speech (which eventually will affect some 80% of patients), as dysarythria can lead to impaired communication, isolation, frustration and low self-esteem.[2] It is a disease that is also very distressing for family and carers.

The quality of life experienced by someone with ALS varies greatly from person to person even when they have the same objective functional impairment.[13] This is, in part, due to the individual's attitudes and values and, in part, to the degree of social support and care they receive.[67] A patient with MND was quoted in *The Times* on 25 July 2000, "...care providers don't seem to understand how quickly this disease moves. If you need a stairlift, you need it now, not in 6 months."[67]

Riluzole is not a cure for ALS nor does it improve a patient's symptoms. The evidence suggests that it may extend time to tracheostomy or death by about 3 months and may slow the rate of deterioration of function, and thus delay the inevitable. Even if riluzole is used, it is no substitute for good quality supportive and palliative care that is rapidly responsive to the changing needs of the patient.

Riluzole is not without side-effects and about 25% of patients withdrew from treatment in the trials. Since, at best, riluzole can only extend life and does not improve symptoms, the decision about whether treatment is worthwhile can only be made from the individual patient's perspective. A patient's physical condition and, more importantly, his or her subjective valuation of the quality of life that this imparts must be taken into account and this should be in a context of optimal symptom control and supportive care.

There is ample evidence that some people with ALS may not wish for their lives to be extended without improvement in their condition. Many have argued for access to physician-assisted suicide.[68] Ganzini and colleagues (1998)[12] reported that over half of a sample of 100 patients with ALS said they would consider assisted suicide. Of these patients, most said that if physician-assisted suicide were legal they would request a lethal prescription and keep it for future use, although, only one person said they would use the prescription immediately. Caregivers generally shared the same attitude to assisted suicide.

The fact that some people either do not wish for their lives to be extended or do not think the side-effects of riluzole are worth the gains is confirmed in a study by Rudnicki (1997).[69] This study found that when riluzole was discussed with 46 patients with probable or definite ALS, only 17 chose to take the drug and 29 refused to take it. When giving explanations as to why they had refused it, 14 said it offered insufficient benefit, nine cited high cost, eight did not wish to prolong their lives, two felt the potential side-effects were not worth the gain, one was in another study and one refused because it offered no gain in quality of life. Patients who had had a shorter duration of either symptoms or confirmed ALS were more likely to take riluzole. Some patients had already participated in trials of alternative drugs such as interleukin growth factor-1 or brain-derived neurotrophic factor, and these patients were less likely to accept riluzole.

It was suggested that the way information is conveyed about riluzole to the patient could also have an effect on their decision as to whether or not to take it. The author reported that patients expressed concern that any prolongation of life would happen at the end of their life, when

functional status was poor. The study concluded that, "…many ALS patients do not just wish to live longer, they want to live better". The Danish Institute for Health Services Research (1998)[13] undertook an in-depth qualitative study of ALS patients and riluzole. They interviewed 12 patients, 10 of whom had chosen to take riluzole and two who had refused it. Eight relatives and six clinicians were also interviewed. It reported that ALS sufferers find themselves doubly in a powerless position – firstly because they have the disease, and secondly because treatment options are so limited:

> "You hang onto life for as long as you can, but I don't want to feel awful whatever the price. Even if it might prolong my life by 2 or 3 months, I'll turn around and ask: what sort of 2 or 3 months they'll be, when I come to the end of it all."[13]

This study confirmed that for some patients the harms of the treatment outweighed the potential benefit. The two people that had refused riluzole felt that the potential side-effects were not worth the possibility of just 2–3 months of extra life.

Of those taking the drug, some patients did not experience side-effects and others were affected by them to varying degrees. Four patients suffered side-effects that were so severe that they discontinued their treatment, and others experimented with dosage to try and overcome side-effects. Both physicians and patients found it hard to distinguish the benefits and harms of the treatment from the natural disease process itself.

For some patients, the need to have some hope or to be taking positive action against the disease were very important, even when they had a realistic understanding about the limited benefits riluzole could offer. This was particularly manifest in those that valued their current lives:

> "…I'm willing to try more or less anything…there was something to win and nothing to lose"
>
> "I'd been told it could prolong your life. That was the reason why I said yes"
>
> "If I'd said no, then once a few years had gone by, and I'd got worse, I would have risked having to sit there and say to myself, 'You were stupid'…it would be stupid to say no"
>
> "…if it can delay it for the time being, so you don't collapse totally, then you might as well go ahead and take it…"

Even patients who did not wish to take the drug wanted the option to be available.[67] Some patients took riluzole in the hope of contributing to research and increasing understanding, rather than for their own sake:[13]

> "you can see how research leads to progress in a lot of other areas. And so it will here. But of course I'll be long dead before then. But that's really a secondary consideration – there'll be others after me…that's why I agreed to take part. I just think you have to say yes."

The importance for some people of 'doing something' was recently reiterated by Tricia Holmes, Director of Care Development at the MND Association:

> "This is a disease over which we have no control. It takes hold of people and removes their ability to live life as they choose. At the very least this drug [riluzole] gives people with MND the sense that they are doing something, and it offers hope, which is terribly important."[67]

In the Danish study,[13] patients were generally well informed about riluzole and were satisfied with the level of information they had received from health professionals, and faith in clinicians and their recommendation to try riluzole was an important factor for some patients. From the health professionals' perspective, riluzole brought hope where there was previously none, but has limited effect, and has side-effects that may reduce quality of life. One commented:

> "…But if we ask what patients actually gain from this…then I have to admit that they get practically nothing. It's a matter of 3 months more, and we don't know what those 3 months will be like…"[13]

There are no other specific treatments for ALS and some patients and health professionals strongly feel that, on the grounds of equity, this drug should be available for those who want it.

Clearly, uptake rates are going to be influenced by the information about the drug and the way it is imparted to patients. If patients with ALS are given accurate, accessible information about riluzole, many will choose not to take it, either because they do not wish to extend their lives without improvement in their symptoms, or because they do not think the limited extension of life is worth the harms and costs. Uptake rates could be as low as 30–40% if the findings of Rudnicki's study[69] are generalisable, however, this study was carried out in the USA where the drug cost may have had a greater influence on the refusal of the medication than it would in the UK. For other patients, any hope or opportunity to fight against this incurable disease is vitally important. Both these facts mean that

using average patient-derived quality-of-life scores for the health states associated with ALS, even if it is assumed that the extension of life occurs in the best of these states, will tend to underestimate the quality of life of those patients who would make an informed choice to use riluzole.

Chapter 6

Potential methodological strengths and weaknesses of the technology assessment

Strengths

This review has systematically sought and incorporated data from all published and unpublished sources identified. It has used all existing data available, and several experts were contacted in an effort to identify unpublished data. It also includes one trial not incorporated in any previous published systematic reviews.

HRs were used to combine the survival data, which is the only method that takes into account all of the available information. The economic analysis involved a rigorous assessment of the strengths and weaknesses of existing analyses, and built a further model to explore the impact of uncertainties revealed.

Weaknesses

Publication bias

Although several experts were contacted to identify unpublished data, it cannot be guaranteed that all unpublished studies were found. There is some evidence of publication bias in the studies reported in this review. The two 'positive' trials were published in the *New England Journal of Medicine* and the *Lancet* (with 155 and 959 patients, respectively), one 'negative' trial (n = 168) remains unpublished and the other was published only in Japanese (n = 195).

Missing data

Further unpublished survival data were produced for the study by Lacomblez and colleagues (1996),[43] and results for tracheostomy-free survival were analysed by Yanagisawa and co-workers,[45] but these were not reported in sufficient detail for estimates to be included in this report. An analysis of individual patient data from all four of the trials identified in this review was carried out at the request of the EMEA,[57] but the full data have not been published.

Update: the above items were received from the company after this report was completed. The new data are addressed in the update section at the end of the report.

Quality of existing data

No survival data beyond 18–21 months were available. Since placebo patients were offered riluzole at the end of the follow-up periods in each of these trials, long-term comparative data would be difficult to interpret, even if available. Although there were four trials, all were small with none having more than 244 patients in any one randomised arm.

There is limited information on the effectiveness of riluzole at the lower dose (50 mg daily), and no evidence that this is less effective than the current recommended dose of 100 mg daily.

There is also little indication of the clinical importance of changes observed in the functional scales, very limited data on the impact on quality of life, and no comparative data. In addition, no cost data were collected in any of the RCTs.

Chapter 7

Discussion and conclusions

Implications of assessment findings

There is limited evidence of a modest increase in tracheostomy-free survival for patients taking riluzole. However, the evidence is restricted and uncertainty remains as to the true size of any effect due to riluzole.

When costs and health economic impact are considered by extrapolating survival beyond that observed in trials, the uncertainties about whether any benefits are worth the costs are magnified. Even under the most optimistic assumptions, riluzole at best postpones death for just a few months, and does not preclude the need for supportive care and practical help.

Implications for the NHS

The evidence on effectiveness and health economic impact does not unequivocally indicate the use of riluzole in ALS as the best policy for the NHS. However, policy makers may wish to take into account the fact that riluzole is the only specific treatment currently available for ALS. If riluzole is available, it is important for patients to be given accurate information about its possible benefits and detriments, so that their final decision can be based on individual preferences. If riluzole is available on the NHS, about 2250 patients could receive it (since the estimated ALS population is 3000, of which 25% would have contraindications). Many of these people, given accurate information about the likely benefits, may choose not to take it. If all these patients did opt for riluzole treatment, it would amount to a cost for the NHS of approximately £8.4 million per year, which is £5.9 million above current expenditure on riluzole. The total additional annual cost to a district of 500,000 residents would be about £50,000.

Whether or not riluzole is used, good supportive care, including practical measures to assist activities of daily living that are timely and responsive to the rapidly changing needs of the patients, remains essential.

Implications for patients and carers

Patients and carers should be given accurate information on the current evidence of the effectiveness of riluzole, and should be aware that riluzole does not cure ALS and may not alter quality of life. The evidence suggests that it may postpone death or tracheostomy by a few months, and there may be some small reduction in the rate of deterioration of functional status.

Implications for future research

Main uncertainties identified

- The size of any effect on survival, particularly in the longer term
- The effect on functional status
- The impact on quality of life
- Consequent uncertainty on health economic impact.

Research in progress

Miller and colleagues (2000)[70] have reported some early results from the ALS patient care database in the USA. This was set up to provide neurologists with data to evaluate and improve their practices, examine temporal trends in the care of patients with ALS and develop hypotheses to be tested in formal clinical trials. The database is a large observational study, not a controlled trial. The Health Services Research Unit at the University of Oxford is undertaking similar studies. Their ALS health profile and the ALS quality-of-life scale studies aim to develop and validate a disease-specific health profile questionnaire and quality-of-life scale, respectively, for ALS.[71–73]

We understand that two trials by Sanofi Recherche investigating SR57746A, a novel agent in the treatment of MND, are in progress. Both trials evaluate SR57746A against placebo, and in one trial all subjects are also taking riluzole.[74] Results are expected at the end of 2000. A study in the Netherlands is investigating the possible relationship between plasma and serum levels of riluzole and the level of cytochrome p450 1A2 activity, as well as the correlation between serum levels and side-effects. A further study in the Netherlands has recently started recruiting 200 patients to examine the effect of plasma and serum concentration of riluzole on disease progression and survival of patients with ALS (Groeneveld GJ, Amsterdam: personal communication, 10 July 2000). In addition, a range of studies which aim to explain

ALS from an epidemiological perspective, or using surrogate markers are planned or underway.[21]

Other than those already identified, we are not aware of other clinical trials of riluzole in ALS, either underway, in progress or abandoned.[21] None of the identified research in progress directly addresses the uncertainties we have identified.

Suggestions for future research

Ideally, reliable information to address the uncertainties highlighted in this report would come from further trials. These RCTs should have survival follow-up through to death, include a substantial incident population and the collection of health economic and quality-of-life data in parallel. The likely individual variability of the latter will need to be carefully considered. Additional questions that might be addressed in such trials include whether there is a difference between short-term (e.g. 1 year) and lifetime use of riluzole and whether 25 mg twice daily is as effective as 50 mg twice daily.

The feasibility of such trials might be doubted. However, there are about 120,000 newly diagnosed cases of ALS per year worldwide, and over 1 million patients will have been diagnosed since the first trial started recruiting 10 years ago. Furthermore, patient perspectives suggest that lack of willingness to participate in such research may not be a barrier. Given these facts, it is disappointing that more and larger trials have not already been conducted.

Even if such trials were commenced now, it will be many years before further information will be made available. In the interim, uncertainty may be partly reduced by information from:

- new data on variation in uptake arising from varying clinician and patient views
- individual patient data meta-analyses of existing trial data to allow full examination of effects within subgroups and a more sensitive examination of effects on functional status
- existing ALS databases to allow more accurate extrapolation beyond observed survival in trials, both for patients treated with riluzole and those not treated
- further data on past trial patients in riluzole arms to observe survival beyond 18 months.

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Antony Stewart was the main author, and designed the protocol and piloted and modified the forms used for assessment of eligibility, validity and data extraction. He undertook searches for studies and requested further information from authors. He liaised with content experts in the field to obtain background information and support. He assessed studies for eligibility and validity, and extracted and collated data from them. Amanda Burls was the main editor. She advised on the protocol for the review, and assessed studies for their eligibility and validity, and independently extracted data from them. She also read and commented on the draft report. Josie Sandercock provided statistical advice, independently extracted data on clinical effectiveness from the studies included in the review, and contributed to the clinical effectiveness sections of the results. She also read and commented on the draft report. Stirling Bryan provided health economics advice, and carried out economic modelling. He contributed to the health economics section, and read and commented on the draft report. Chris Hyde advised on the protocol for the review and contributed to the discussion and conclusions section, and, in addition, read and commented on the draft report. Pelham Barton advised on the models used for economic analyses and carried out mathematical modelling for the health economics results section. He also read and commented on the draft report. Finally, Anne Fry-Smith advised on the search strategy, and read and commented on the draft report.

References

1. Swash M. Clinical features and diagnosis of amyotrophic lateral sclerosis. In: Brown RH, Meininger V, Swash M, editors. Amyotrophic lateral sclerosis. London: Martin Dunitz; 2000. p. 3–30.

2. Motor Neurone Disease Association. Motor neurone disease: a problem solving approach for general practitioners and the primary health care team. Northampton: Motor Neurone Disease Association; 1998.

3. International Alliance of ALS/MND Associations on the Internet. URL: http://www.alsmndalliance.org/

4. Shaw P. Clinical review; science, medicine and the future: motor neurone disease. *BMJ* 1999;**318**: 1118–21.

5. Haslett C, Chilvers ER, Hunter JAA, Boon NA, editors. Davidson's principles and practice of medicine. 18th ed. London: Churchill Livingstone; 1999. p. 991–3.

6. Brooks BR. Defining optimal management in ALS: from symptoms to announcement. *Neurology* 1999;**53** (Suppl 5):S1–3.

7. Chancellor AM. Diagnosing motor neurone disease (editorial). *BMJ* 1996;**312**:650–1.

8. Swash M. An algorithm for ALS diagnosis and management. *Neurology* 1999;**53** (Suppl 5):S58–62.

9. Dubrovsky AL, Sica REP. Current treatment pathways in ALS: a South American perspective. *Neurology* 1999;**53** (Suppl 5):S11–16.

10. Brooks BR. Subcommittee on motor neuron diseases/amyotrophic lateral sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases. El Escorial "Clinical limits of amyotrophic lateral sclerosis" Workshop contributors. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. *J Neurol Sci* 1994;**124** (Suppl): 96–107.

11. Brooks BR. What are the implications of early diagnosis? Maintaining optimal health as long as possible. *Neurology* 1999;**53** (Suppl 5):S43–5.

12. Ganzini L, Johnson WS, McFarland BH, Tolle SW, Lee MA. Attitudes of patients with amyotrophic lateral sclerosis and their care givers toward assisted suicide. *N Engl J Med* 1998;**339**:967–73.

13. Danish Institute for Health Services Research and Development. Between hope and despair: ALS patients and riluzole. Copenhagen: Danish Institute for Health Services Research and Development; 1998. Report no.: DSI Rapport 98.03.

14. Chancellor AM, Slattery JM, Fraser H, Swingler RJ, Holloway SM, Warlow CP. The prognosis of adult-onset motor neuron disease: a prospective study based on the Scottish motor neurone disease register. *J Neurol* 1993;**240**:339–46.

15. Stambler N, Charatan M, Cedarbaum JM. Prognostic indicators of survival in ALS. *Neurology* 1998;**50**:66–72.

16. Kondo K, Hemmi I. Clinical statistics in 515 fatal cases of motor neuron disease: determinants of course. *Neuroepidemiology* 1984;**3**:129–48.

17. Shneerson JM. Motor neurone disease: some hope at last for respiratory complications (editorial). *BMJ* 1996;**313**:244–5.

18. O'Brien T, Kelly M, Saunders C. Motor neurone disease: a hospice perspective. *BMJ* 1992;**304**:471–3.

19. Oliver D. Death from motor neurone disease can be peaceful [letter]. *BMJ* 1995;**310**:1466–7.

20. Roberts J. Riluzole may help survival in motor neurone disease [news]. *BMJ* 1994;**308**:678.

21. Aventis Pharma. [Industry submission to the National Institute of Clinical Excellence]. Unpublished; 2000.

22. Tomik B, Nicotra A, Ellis C, Parton M, Shaw CE, Leigh PN. Ethnic differences in MND: a case control study [abstract]. Proceedings of the Motor Neurone Disease Association 10th International Symposium on ALS/MND; 1999 Nov 15–19; Vancouver, Canada. Northampton: Motor Neurone Disease Association; 1999. p. 129.

23. Health episode statistics for England 1997–8. London: Department of Health; 1998.

24. Vogels OJM, Oyen WJG, Van Engelen BGM, Padberg GWAM, Horstink MWIM. Decreased striatal dopamine-receptor binding in sporadic amyotrophic lateral sclerosis: glutamate hyperactivity? *Neurology* 1999;**52**:1275–7.

25. Buckley J, Warlow C, Smith P, Hilton-Jones D, Irvine S, Tew JR. Motor neuron disease in England and Wales, 1959–1979. *J Neurol Neurosurg Psychiatry* 1983;**46**:197–205.

26. Mitsumoto H. Riluzole – what is its impact in our treatment and understanding of amyotrophic lateral sclerosis? *Ann Pharmacother* 1997;**31**:779–81.

27. Riluzole for amyotrophic lateral sclerosis. *Drug Ther Bull* 1997;**35**:11–12.

28. Doble A. The pharmacology and mechanism of action of riluzole. *Neurology* 1996;**47** (Suppl 4): 233–41.

29. Jackson M, Rothstein JD. Excitotoxicity in amyotrophic lateral sclerosis. In: Brown RH, Meininger V, Swash M, editors. Amyotrophic lateral sclerosis. London: Martin Dunitz; 2000. p. 263–77.

30. British National Formulary. London: BMA and The Royal Pharmaceutical Society of Great Britain; 1999 Sept. Report no.: BNF No.38.

31. Booth-Clibborn N, Best L, Stein K. Riluzole for motor neurone disease. Southampton: Wessex Institute for Health Research & Development; 1997. Report no.: DEC Report 73.

32. Haas JF. The tolerability and adverse event profile of riluzole. *Rev Contemp Pharmacother* 1997;**8**:265–73.

33. Miller RG, Rosenberg JA, Gelinas D, Mitsumo H, Newman D Sufit R, *et al.* Practice parameter: the care of the patient with amyotrophic lateral sclerosis (an evidence-based review): report of the quality standards subcommittee of the American Academy of Neurology: ALS practice parameters task force. *Neurology* 1999;**52**:1311–23.

34. Corr B, Frost E, Traynor BJ, Hardimann O. Service provision for patients with ALS/MND: a cost-effective multidisciplinary approach. *J Neurol Sci* 1998;**160** (Suppl 1):S141–5.

35. Dengler R. Current treatment pathways in ALS: a European perspective. *Neurology* 1999; **53** (Suppl 5):S4–10.

36. Aventis Pharma. Press release: Aventis announces unaudited 1999 sales. URL: http://www2.aventis.com/press/pr_047.htm

37. Burls A, Cummins C, Fry-Smith A, Gold L, Hyde C, Jordan R, *et al.* West Midlands Development and Evaluation Service handbook. version 2.2. Birmingham: Department of Public Health and Epidemiology, University of Birmingham; 2000.

38. Deeks J, Glanville J, Sheldon T. Undertaking systematic reviews of research on effectiveness. York: NHS Centre for Reviews and Dissemination; 1996. Report no.: CRD Report No.4.

39. Clarke M, Oxman AD, editors. Cochrane reviewers' handbook 4.0. In: The Cochrane Library. Issue 1 [database on CD-ROM]. The Cochrane Collaboration. Oxford: Update Software; 2000.

40. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**:1286–91.

41. Lacomblez L, Bensimon G, Leigh PN, Guillet P, Powe L, Durrleman S, *et al.* A confirmatory dose-ranging study of riluzole in ALS. *Neurology* 1996; **47** (Suppl 4):S242–50.

42. Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. *N Engl J Med* 1994;**330**:585–91.

43. Lacomblez L, Bensimon G, Leigh PN, Guillet P, Meininger V for the Amyotrophic Lateral Sclerosis Study Group II. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. *Lancet* 1996;**347**: 1425–31.

44. Meininger V, Lacomblez L, Bensimon G. Comprehensive medical report. Unpublished study report; 1995. Report no.: RP 54274-302.

45. Yanagisawa N, Tashiro K, Tohgi H, Mizuno Y, Kowa H, Kimuma J, *et al.* Efficacy and safety of riluzole in patients with amyotrophic lateral sclerosis: double-blind placebo-controlled study in Japan. *Igakuno Ayumi* 1997;**182**:851–66.

46. Riviere M, Meininger V, Zeisser P, Munsat T. An analysis of extended survival in patients with amyotrophic lateral sclerosis treated with riluzole. *Arch Neurol* 1998;**55**:526–8.

47. Sojka P, Anderson PM, Forsgren L. Effects of riluzole on symptom progression in amyotrophic lateral sclerosis. *Lancet* 1997;**349**:176–7.

48. Kalra S, Cashman NR, Genge A, Arnold DL. Recovery of N-acetylaspartate on corticomotor neurons of patients after riluzole therapy. *Neuroreport* 1998;**9**:1757–61.

49. Gawel MJ. Reduction in mortality from ALS with riluzole. Unpublished study; 1999.

50. Arriada-Mendicoa N, Otero-Siliceo E, Burbano G, Corona-Vazquez T. Open label study of riluzole for the treatment of amyotrophic lateral sclerosis. *Revista Ecuatoriana de Neurologia* 1999;**8**:33–6.

51. Desiato MT, Palmieri MG, Giacomini P, Scalise A, Arciprete F, Caramia MD. The effect of riluzole in amyotrophic lateral sclerosis: a study with cortical stimulation. *J Neurol Sci* 1999;**31**:98–107.

52. Pongratz D, Neundorfer B. Open-label trial of riluzole 50 mg b.i.d. in treatment of amyotrophic lateral sclerosis (ALS). *Aktuelle Neurologie* 1999;**26**:225–9.

53. Couratier P, Druet-Cabanac M, Truong CT, Bernet-Bernady P, Dumas M, Vallat JM, *et al.* Intérìts d'une base de données informatisée dans le diagnostic et le suivi de patients atteints de la sclérose latérale amyotrophique. *Rev Neurol (Paris)* 2000;**156**:357–63.

54. Chilcott J, Golightly P, Jefferson D, McCabe CJ, Walters S. The use of riluzole in the treatment of amyotrophic lateral sclerosis (motor neurone disease). Sheffield: Working Group on Acute Purchasing, Trent Institute for Health Services Research; 1997. Guidance note for purchasers 97/3.

55. Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neurone disease (MND). In: The Cochrane Library. Issue 2 [database on CD-ROM]. Oxford: Update Software; 2000.

56. Aventis Pharma. [Letter to the National Institute of Clinical Excellence]. Unpublished; 2000.

57. Committee for Proprietary Medicinal Products. European Public Assessment Report (EPAR). Rilutek. London: The European Agency for the Evaluation of Medicinal Products, 1999. Report no.: CPMP/290/96.

58. Assman SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet* 2000;**355**:1064–9.

59. Riluzole vs. usual care in the treatment of ALS. An international economic evaluation. Montreal: Benefit Research Group; 1996. Report no.: IRPR12 Final Report. Version 1.

60. Gray AM. ALS/MND and the perspective of health economics. *J Neurol Sci* 1998;**160** (Suppl 1):S2–5.

61. Ginsberg GM, Lev B. Cost–benefit analysis of riluzole for the treatment of amyotrophic lateral sclerosis. *Pharmacoeconomics* 1997;**12**:578–84.

62. Messori A, Trippoli S, Becagli P, Zaccara G on behalf of the Italian Cooperative Group for the Study of Meta-Analysis and the Osservatorio SIFO sui Farmaci. Cost effectiveness of riluzole in amyotrophic lateral sclerosis. *Pharmacoeconomics* 1999;**16**:153–63.

63. Tavakoli M, Davies HTO, Malek M. Modelling the long-term cost-effectiveness of riluzole for the treatment of amyotrophic lateral sclerosis. *J Drug Assessment* 1999;**2**:219–32.

64. Dolan P. Modelling valuations for EuroQol health states. *Med Care* 1997;**35**:1095–108.

65. Munsat TM, Riviere M, Swash M, Leclerc C. Economic burden of amyotrophic lateral sclerosis in the United Kingdom. *J Med Economics* 1998; **1**:235–45.

66. Cox DR, Oakes D. Analysis of survival data. London: Chapman & Hall; 1984.

67. Dooley D. I deserve a life, too. *The Times* 2000 Jul 25; Sect. Times 2 Health, p. 10–11.

68. Doyal L. The case for physician-assisted suicide and active euthanasia in amyotrophic lateral sclerosis. In: Brown RH, Meininger V, Swash M, editors. Amyotrophic lateral sclerosis. London: Martin Dunitz; 2000. p. 423–39.

69. Rudnicki SA. Factors influencing a patient's decision regarding riluzole: an early experience. *J Neurol Sci* 1997;**152** (Suppl 1):S80–1.

70. Miller RG, Anderson FA Jr, Bradley WG, Brooks BR, Mitsumo H, Munsat TL, *et al.* The ALS patient care database: goals, design, and early results. ALS C.A.R.E. Study Group. *Neurology* 2000;**11**:53–7.

71. Jenkinson C, Brennan C, Fitzpatrick R, Swash M, Greenhall R. The development and validation of the Amyotrophic Lateral Sclerosis Quality of Life Scale. Oxford: Health Services Research Unit. URL: http://hsru/dphpc.ox.ac.uk/alsqls.htm

72. Jenkinson C, Peto V, Fitzpatrick R, Swash M. The European amyotrophic lateral sclerosis health profile study. Oxford: Health Services Research Unit. URL: http://hsru.dphpc.ox.ac.uk/als.htm

73. Jenkinson C, Fitzpatrick R, Brennan C, Bromberg M, Swash M. Development and validation of a short measure of health status for individuals with amyotrophic lateral sclerosis/motor neurone disease: the ALSAQ-40. *J Neurol* 1999;**246** (Suppl):16–21.

74. Motor Neurone Disease Association. Information sheet No.G. SR57746A: questions and answers. Northampton: Motor Neurone Disease Association; 1998.

75. Brinkman JR, Andres P, Mendoza M, Sanjak M. Guidelines for the use and performance of quantitative outcome measures in ALS clinical trials. URL: http://www.wfnals.org/Articles/quantitative.htm

76. Norris FH, Calanchini PR, Fallat RJ, Panchari S, Jewett B. The administration of guanidine in amyotrophic lateral sclerosis. *Neurology* 1974; **24**:721–8.

77. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998;**17**:2815–34.

78. Rhône-Poulenc Rorer. Riluzole®. Volume 1: follow-up measures. Unpublished; 1997 Jul 31.

79. DATA: Decision Analysis by TreeAge. Williamstown, MA: TreeAge Software, Inc.

Appendix 1

Advisory group of experts consulted

Advisory group of experts consulted and why they were approached

Dr R Miller	Main author of Cochrane Systematic Review on this topic, expertise in this area
Dr K Wheatley	Deputy Director of Birmingham Trials Unit, statistical expertise with specialist interest in riluzole
Dr A Al-Chalabi	Researcher with specialist interest in ALS
Dr G Ginsberg	Health economist with specialist interest in riluzole

Possible competing interests

Dr Miller has accepted speaker's honoraria from several pharmaceutical companies, including Rhône-Poulenc Rorer, the manufacturer of riluzole. He was an investigator in the trial by Lacomblez and colleagues (1996),[43] but did not participate in data analysis or manuscript preparation. He was also the main author of a previous systematic review.[55]

Dr Wheatley has attended a meeting of the UK MND Advisory Panel, the expenses of which were paid by Excerpta Medica UK, however, the offered honorarium was declined. He is also preparing an independent review of riluzole.

Dr Al-Chalabi received a payment from Rhône-Poulenc Rorer towards travel/subsistence costs for an academic meeting in 1996, and has attended various meals sponsored by the company. He was awarded the 1999 Charcot Young Investigator for Research into ALS, which was co-sponsored by Rhône-Poulenc Rorer. The department in which he works was one of the centres running the original trials into riluzole, and applies for scientific and educational grants from Rhône-Poulenc Rorer.

Dr Ginsberg presented a paper at two GP forums in England, for which the expenses were paid by Rhône-Poulenc Rorer.

Appendix 2

List of clinical experts and specialist organisations contacted

Dr A Al-Chalabi	*Medical Research Council Clinician Scientist, Institute of Psychiatry, London, UK*
Professor D Brooks	*Consultant Neurologist, Hammersmith Hospital, London, UK*
Dr G Ginsberg	*Health Economist, Ministry of Health, Jerusalem, Israel*
Dr D Jefferson	*Consultant Neurologist, Queen's Medical Centre, Nottingham, UK*
Professor N Leigh	*Consultant Neurologist, Institute of Psychiatry, London, UK*
Dr R Miller	*Chairman of the Department of Neurology, California Medical Center, San Francisco, USA*
Professor D Mitchell	*Consultant Neurologist, Royal Preston Hospital, Preston, UK*
Dr HS Pall	*Consultant Neurologist, Queen Elizabeth Hospital, Birmingham, UK*
Professor M Swash	*Consultant Neurologist, The Royal London Hospital, London, UK*
Dr K Wheatley	*Deputy Director of Birmingham Trials Unit, Birmingham, UK*
MND Association	*Northampton, UK*

Appendix 3

Conference abstracts obtained

4th International Symposium on ALS/MND; 1993 Nov 25–27; Chantilly, Paris, France.

11th Tokyo Metropolitan Institute for Neuroscience International Symposium; 1995 Oct 25–27; Tokyo, Japan.

Association of British Neurologists Symposium; 1996 Sept 18; London, UK.

7th International Symposium on ALS/MND; 1996 Nov 11; Chicago, USA.

Meeting of the European Federation of Neurological Sciences; 1997 Jun 6; Prague, Czech Republic.

8th International Symposium on ALS/MND; 1997 Nov 3–5; Glasgow, UK.

48th European Neuromuscular Centre Workshop on Drug Trials and Clinical Research in ALS; 1997 Jan 12–14; Narden, The Netherlands.

49th American Academy of Neurology Annual Meeting; 1997; Boston, USA.

Scientific Education Partnership/Amyotrophic Lateral Sclerosis Association; 1997 Jan 20–22; Missouri, USA.

Conference on Current Issues in ALS Therapeutic Trials; 1998 Apr 2–4; Virginia, USA.

9th International Symposium on ALS/MND; 1998 Nov 16–18; Munich, Germany.

10th International Symposium on ALS/MND; 1999 Nov 15–17; Vancouver, Canada (full abstract book obtained).

Appendix 4

Functional scales for ALS

The original Norris scale combines ratings for a total of 34 parameters, consisting of 22 functional parameters, plus reflex activity, fasciculations, atrophy, etc. Functional ratings are defined only as normal, impaired, trace or zero, and may be insensitive to change.[75] The Norris scale has a maximum score of 100 (*Table 16*);[76] the lower the score, the worse the functional state.

The trial by Lacomblez and colleagues[43] used a modified Norris scale, which is subdivided into categories for manual muscle testing, bulbar function and limb function (*Table 17*). Each item of upper and lower limb is scored for the right and left side separately.

TABLE 16 *ALS scoring system, showing example scoring (from Norris and colleagues, 1974[76])*

Item	Weight			
	3 (normal)	**2 (impaired)**	**1 (trace)**	**0**
Hold up head	X			
Chew food	X			
Swallow	X			
Speak	X			
Turn in bed	X			
Sit up	X			
Empty bowel/bladder	X			
Breathe	X			
Cough	X			
Write name		X		
Use buttons, zippers		X		
Feed self		X		
Grip-lift self	X			
Lift book or tray	X			
Lift fork, pencil	X			
Change arm position	X			
Climb stairs, one flight			X	
Walk one block			X	
Walk across room		X		
Walk with assistance	X			
Stand up	X			
Change leg position	X			
Stretch reflexes:		Hyper/hypo	Absent	Clonic
– Arms		X		
– Legs		X		
	Absent	Present	Hyper	Clonic
Jaw jerk	X			
Plantar responses:	Flexor	Mute	Equivocal	Extensor
– Right				X
– Left				X
	None	Slight	Moderate	Severe
Fasciculation		X		
Wasting:				
– Face, tongue	X			
– Arms, shoulders		X		
– Legs, hips		X		
Labile emotions	X			
			0 to mild	Moderate to severe
Fatigability			X	
Leg rigidity			X	
Totals in example (81)	57	22	2	0
Theoretical totals (100)	96	4	0	0

TABLE 17 *Functional scales for ALS (taken from Lacomblez and colleagues[41])*

Manual muscle testing	**Modified Norris bulbar scale**	**Modified Norris limb scale**
I. Upper limb strength[a] Thumb opposition Wrist flexion Wrist extension Elbow flexion Elbow extension Shoulder abduction	Blow Whistle Blowing out cheeks Jaw movement Clicking tongue Tongue protrusion Tongue against the cheek Tongue against the palate Cough Hypersialorrhea Nasalisation Speech: mumbling Swallowing: food	Hold up head Turn in bed Sit up in bed Writing ability Buttoning, zipping Dress oneself with a shirt/blouse Dress oneself with pants/skirt Cutting meat Holding a fork Filling up a glass and drinking from it Standing up and shaking hands Combing one's hair Brushing one's teeth Lift book or tray Lift fork or pencil Change arm position Climb stairs Walk around a block Walk alone Walk with assistance Stand up
II. Lower limb strength[a] Ankle dorsiflexion Knee flexion Knee extension Hip flexion		
III. Neck Neck flexion Neck extension	Gradation of items 1 to 9: None Moderate Impaired Normal	
Gradation of items: No contraction Flicker of trace contraction Active movement with gravity eliminated Active movement against gravity but not against resistance Active movement against gravity and resistance Normal power	Gradation of items 10 to 12: Severe Present Moderate Absent	Gradation of terms: None Moderate Impaired Normal
	Gradation of item 13: 1/2 Liquid Minced Tender Normal (If food is given through gastric tube, swallowing must be rated 0)	

[a] *Each item of upper and lower limb is scored for the right and left side separately*

Appendix 5

Survival data extraction

The appropriate summary statistic for use with survival (time to event) data is the HR, which summarises the difference between two Kaplan–Meier survival curves and represents the overall relative risk of death over the period of follow-up of patients. This is preferable to simple comparisons of the overall number of events or the odds of survival at fixed timepoints.[77]

In order to combine survival data from different trials, an estimate of the log HR and its variance for each trial is needed. The pooled HR and associated 95% CI are calculated (using the fixed-effects model) as follows:

$$\ln\,(HR) = \frac{\sum\left(\frac{\ln\,(HR_i)}{Var\,[\ln\,(HR_i)]}\right)}{\sum\left(\frac{1}{Var\,[\ln\,(HR_i)]}\right)}$$

$$Var\,[\ln\,(HR)] = \frac{1}{\sum\left(\frac{1}{Var\,[\ln\,(HR_i)]}\right)}$$

The pooled HR and associated 95% CI are given by:

$$\exp\left\{\ln\,(HR) \pm 1.96\sqrt{Var\,[\ln\,(HR)]}\right\}$$

Information available from trial reports

Although the log HR and its variance are rarely reported directly, these may be estimated from the HR and an associated 100 (1–α)% CI as follows:[77]

$$Var[\ln\,(HR)] = \left(\frac{\ln\,(Upper\ CI) - \ln\,(Lower\ CI)}{2 \times z_{(1-\alpha/2)}}\right)^2$$

Estimating the HR where it is not reported

Where no estimate of the HR, or the uncertainty surrounding this estimate, is given, methods are available to estimate these from the published Kaplan–Meier survival curves.[77] However, in this case all of the survival curves in each of the trial reports were accompanied by a summary of the number of patients 'at risk' (i.e. still alive and with follow-up) at the start of each 3-month interval (up to 18 or 21 months) and the number of patients dying within each of these intervals. The numbers censored (known to be alive at last follow-up) within each interval may thus be calculated. We have used these figures to estimate summary survival statistics using the usual log-rank method and the Mantel–Haenszel estimates of the log HR and its variance.

The log-rank method accounts for censoring between but not within intervals, i.e. it assumes that individuals who are censored at a particular timepoint lived longer than individuals who died at the same timepoint. For this assumption to be reasonable, the raw data should be recorded in 'short' time intervals (e.g. hour, day or month of death, depending on the context). In this case, we are not analysing raw data, but rather we are trying to approximate the raw (individual patient) data from these trials using the summary information given with the Kaplan–Meier survival curves. In using the usual log-rank method, we are effectively assuming that, in the original data sets, all patients censored within each 3-month interval were censored at the end of the interval, whilst all the deaths within the interval occurred at some earlier point in the interval. Clearly, this assumption may not accurately reflect the original data set. Thus, in order to investigate the reliability of this method, we performed the calculation for all Kaplan–Meier summary data presented in each trial, even where the HR and a 95% CI were adequately reported; where data are available from both sources, the estimates may be compared. Our estimates, along with the data available from the trial reports, are summarised in appendix 8.

Despite using summary data at 3-month intervals, our estimates seem to be reasonably consistent with the published information when there are data available from both sources. We are not aware of any methodological literature on an 'actuarial' approach to the log-rank method where time intervals are 'long', but we also examined estimates derived from a simple 'actuarial' approach (making

some allowance for censoring within intervals). Where they differed to any degree, these estimates tended to perform rather worse than those derived without any allowance for censoring within intervals. This may be due to the particular trials included here. The common approach in these trials seems to have been to follow-up patients for a specified period of time (18 months) rather than to follow-up all patients until an event was observed. All of the trials report very little loss of follow-up prior to 15 months. Under these circumstances, a simple adjustment that assumes that censoring is uniform throughout the interval may over-compensate for heavy censoring within the last two intervals. Whatever the reason, the usual log-rank approach seems to work well for this group of trials, although it might be less reliable for trials with a different pattern of follow-up.

The results presented in chapter 3 are those presented directly in the trial report where available; estimates derived from the Kaplan–Meier summary data are used where the information is not directly available from the trial report.

Appendix 6

Summary of systematic reviews identified

Three previous systematic reviews have been published,[31,54,55] as well as a marketing authorisation report that evaluated all four of the trials included in this review.[57] Booth-Clibborn and co-workers (1997)[31] included trials by Bensimon and colleagues,[42] Lacomblez and colleagues[43] and Meininger and co-workers.[44] The marginal costs of riluzole therapy were described and a number needed to treat of six was calculated for early-stage patients (i.e. six patients would need to be treated with riluzole to delay one death or tracheostomy to beyond 18 months). They estimated the lifetime cost of riluzole treatment to be £11,000– £19,000, assuming 3–5 years of survival. As it costs £33,500 to treat six patients with riluzole for 18 months, this would be the cost of preventing one death or tracheostomy at 18 months. Although they noted that a delay in death or tracheostomy had been observed at 18 months, uncertainties about the duration of the delay and quality of life during this period led to the conclusion that there was insufficient evidence to support riluzole treatment.

Chilcott and colleagues (1997)[54] included trials by Bensimon and co-workers[42] and Lacomblez and co-workers.[43] Their CEA was based on the Lacomblez trial, and focused on the 100 mg treatment group. Two CBAs were performed, one adjusted for differences between prognostic characteristics and the other unadjusted. The cost per life-year gained over 18 months was estimated to be about £50,000, or as low as £22,000. When adjusted for prognostic factors and modelled over 10 years, the estimated mid-range was £27,600. They felt unable to support the funding of riluzole due to the uncertainties in the interpretation and analysis of survival, lack of quality-of-life information, limited claimed benefit and high cost-effectiveness ratio. Miller and colleagues (2000)[55] assessed primary and secondary endpoints of the Bensimon[42] and Lacomblez[43] trials, and performed a meta-analysis. They concluded that the benefits of riluzole (100 mg daily) were modest but definite.

The CPMP of the European Agency for the Evaluation of Medicinal Products produced a European Public Assessment Report (1996, revised 1999),[57] describing a marketing authorisation for riluzole in the European Union. The report incorporated the four trials included in this review. The CPMP reported that riluzole had demonstrated a modest extension of life or the time taken for progression to mechanical ventilation in ALS patients, other than those in the late stages of the disease. Adverse events and side-effects were also reported. The CPMP concluded that riluzole showed adequate evidence of efficacy and a satisfactory risk–benefit profile, and recommended its marketing authorisation. Following authorisation, the CPMP asked the manufacturer to carry out a meta-analysis of individual patient data, including the trial by Yanagisawa and colleagues[45] not previously submitted. Following the evaluation of the meta-analysis, the statistical evidence for the efficacy of riluzole was less secure, but it was felt that the balance of probability was nevertheless in favour of riluzole.

Appendix 7

Summary of clinical effectiveness studies excluded

Riviere and colleagues (1998)[46] re-analysed data from the study by Lacomblez and co-workers[43] using a classification of discrete health states. A significant difference was shown between riluzole and placebo groups in only one (mild) health state. The analysis was post-hoc and is seen as a preliminary study, requiring further confirmation.

Sojka and colleagues (1997)[47] compared symptom progression both before and during administration of 100 mg daily of riluzole, in a case series of five patients with ALS. The effect of riluzole in the patient group was highly variable, ranging from no effect to accelerated progression of symptoms. The authors suggest that ALS patients may not constitute a homogenous group with respect to the efficacy of riluzole treatment. The fact that this is a very small study using neither randomisation nor controls prevents inferential ability, and it is acknowledged that further studies are required. However, the methodology employed may be useful in monitoring disease progression rates on patients treated with riluzole.

Kalra and co-workers (1998)[48] used magnetic resonance spectroscopy to measure the N-acetyl-aspartate:creatine relative resonance intensity ratio in the motor cortex, as a marker for neuronal loss. They reported that 11 patients treated with riluzole 100 mg daily for 3 weeks experienced an increase in the N-acetylaspartate: creatine ratio (indicating a reversal in cortico-motor neuronal loss), compared to a decrease in 12 control patients. The study was non-randomised, using a small sample of patients and short follow-up times.

Gawel (unpublished; 1999)[49] analysed 528 patients with ALS in a single-centre, non-randomised study using historical controls. The clinic was included in the Canadian early access riluzole programme. Most patients with ALS presenting at the clinic since 1995 (n = 159) were given 100 mg daily of riluzole. Demographic characteristics were similar in both groups, except for the fact that a greater proportion of control group patients presented with spasticity. At 12 months, 89% of riluzole patients were still alive, compared to 87% of controls. At 18 months, 77% of riluzole patients were alive, compared with 70% of controls. These results show much higher survival rates than those reported by Bensimon and colleagues (1994).[42] The author suggests this difference in results between studies may reflect the study design, as only newly diagnosed patients were included.

Arrida-Mendicoa and co-workers (1999)[50] carried out an open-label, non-randomised, non-comparative study to evaluate the effect of 100 mg daily of riluzole on clinical progression in 50 Mexican patients with ALS. Patients were assessed using the Jablecki scale, and 31 patients completed the 1-year study. At the end of the study, monthly progression of the disease had decreased significantly both for bulbar and limb onset, and no severe side-effects were recorded. The authors concluded that riluzole can delay disease progression and should be considered for ALS patients. However, they recommend that it should be made clear that ALS cannot be cured, and that economic issues should be taken into account.

Desiato and co-workers (1999)[51] assessed 31 patients with ALS receiving riluzole 100 mg daily and 30 age-matched controls in a 6-month prospective open study, using single and paired transcranial magnetic stimulation. A number of parameters were measured before and after the administration of riluzole. Significant differences were recorded between treated patients and controls in two parameters (the normal behaviour of the silent period duration in response to increasing transcranial magnetic stimulation of treated patients, and the significant reduced size of motor-evoked potential duration in treated patients, compared with controls). The authors concluded that their assessment method might be considered a setting for controlled trials in extended patient series, even in a pre-clinical phase.

Pongratz and colleagues (1999)[52] evaluated the safety of riluzole in an open-label, multinational, uncontrolled trial. The study was conducted between 1995 and 1997, and each patient received 100 mg daily of riluzole for a mean of 7.2 months.

A total of 7916 patients with ALS in 39 countries participated, although the paper concentrates on the 919 patients treated in Germany. Of the German patients, 17.6% died from ALS during the study. The most frequent adverse events were reduced lung function (7.1%), asthenia (5.8%), pneumonia (2.5%) and abdominal pain (2.5%). Serious adverse events attributed to riluzole occurred in 16 patients (1.7%), most of which were changes in liver enzyme, which were reversible and non-fatal. The authors concluded that riluzole is well tolerated, because most adverse events were due to symptoms of ALS, and observed adverse events were lower than those reported in previous studies. The safety profile from the German centres was similar to the total study population.

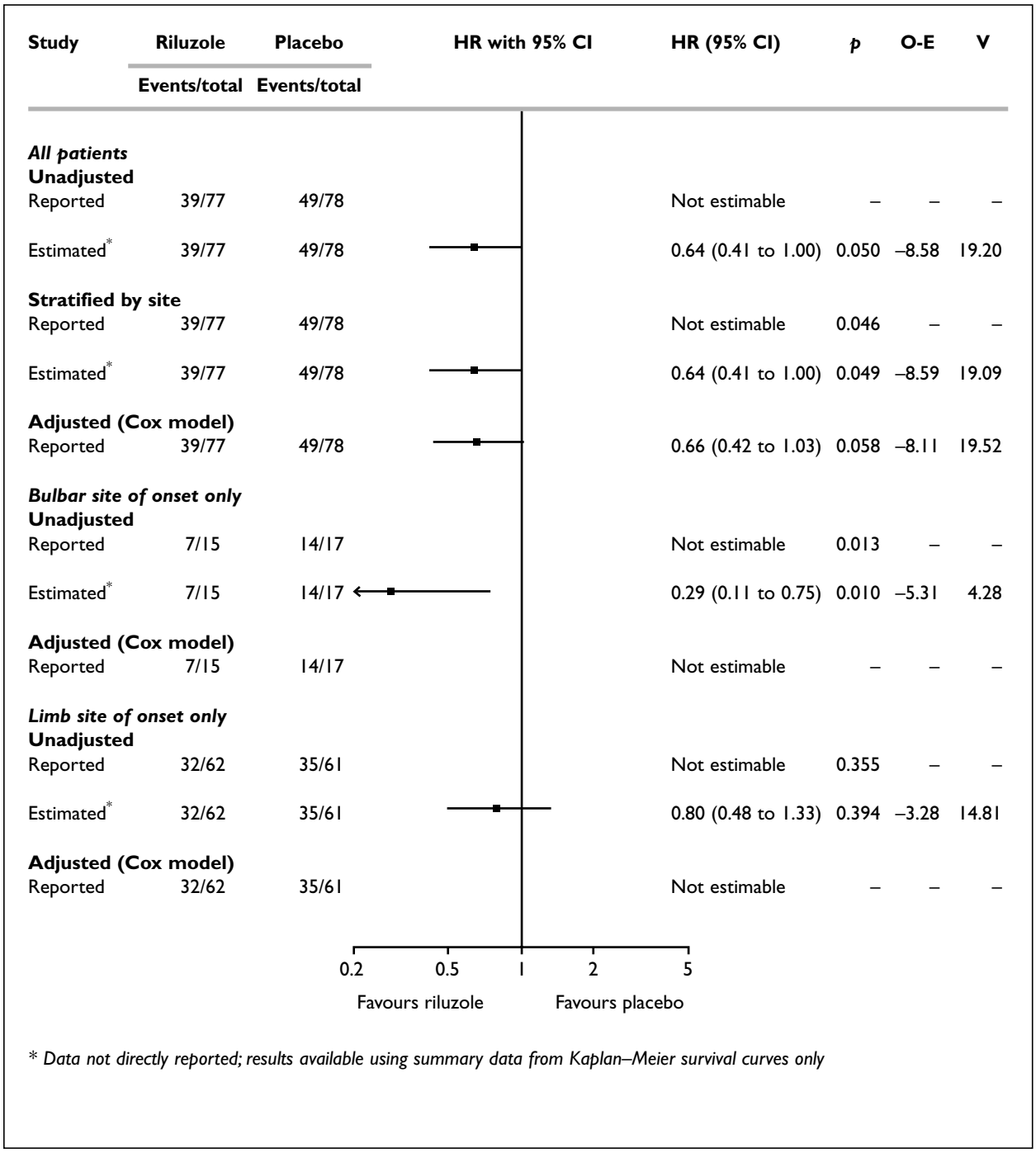
Couratier and colleagues (2000)[53] published a cohort study describing part of the content of a computerised database for patients with ALS. A total of 340 patients were studied, 159 of whom were treated with riluzole. The median survival for riluzole patients was 52 months.

Appendix 8

Results (reported and estimated) from each trial

Survival results reported directly by the authors or estimated from the Kaplan–Meier summary data (see appendix 5) are summarised in *Figures 9–12*. For each result, we have summarised data available directly from the trial report ('reported') and data estimated from the Kaplan–Meier summary data ('estimated'); in some cases only a (log-rank) *p*-value is available from the trial reports and these are included for comparison. The reported/estimated pairs are plotted adjacent to each other on the figures to facilitate comparison where data by both means is available.

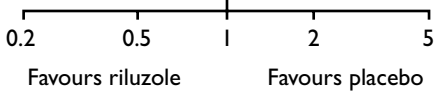
Adjusted estimates derived from the Cox model are also summarised on these plots. The covariates included in the adjusted models are listed in *Table 18*.



* *Data not directly reported; results available using summary data from Kaplan–Meier survival curves only*

FIGURE 9 *Bensimon and colleagues*[42]

Study	Riluzole Events/total	Placebo Events/total	HR (95% CI)	*p*	O-E	V
All patients						
Unadjusted						
Reported	311/717	120/242	Not estimable	–	–	–
Estimated*	311/717	120/242	0.80 (0.63 to 1.01)	0.058	–15.95	71.04
Stratified by site						
Reported	311/717	120/242	0.81 (0.66 to 0.99)	0.048	–19.70	93.47
Estimated*	311/717	120/242	Not estimable	–	–	–
Adjusted (Cox model)						
Reported†	311/717	120/242	0.67 (0.58 to 0.78)	–	–66.10	166.25
By dose						
50 mg						
Reported	106/237	120/242	0.85 (0.66 to 1.10)	0.25	–9.24	56.86
Estimated	106/237	120/242	0.85 (0.64 to 1.12)	0.24	–8.38	50.49
100 mg						
Reported	102/236	120/242	0.79 (0.61 to 1.03)	0.076	–12.86	54.57
Estimated	102/236	120/242	0.79 (0.60 to 1.04)	0.091	–11.89	49.49
200 mg						
Reported	103/244	120/242	0.79 (0.61 to 1.03)	0.075	–13.20	56.00
Estimated	103/244	120/242	0.79 (0.60 to 1.04)	0.094	–11.84	50.05



* *Data not directly reported; results available using summary data from Kaplan–Meier survival curves only*

† *Adjusted results reported for each riluzole arm separately; results presented here are stratified pooled results for all riluzole arms combined*

FIGURE 10 *Lacomblez and colleagues*[43]

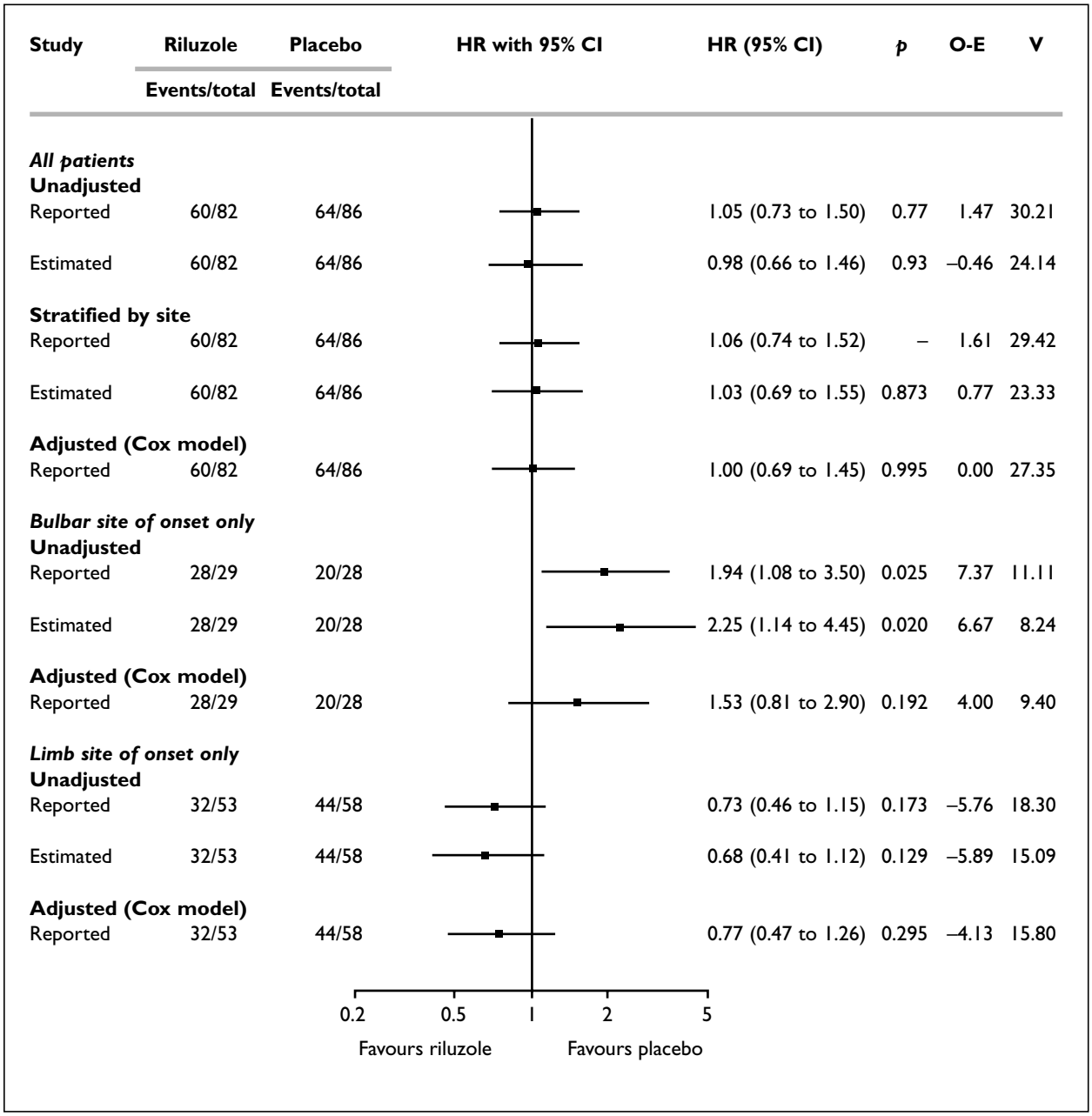
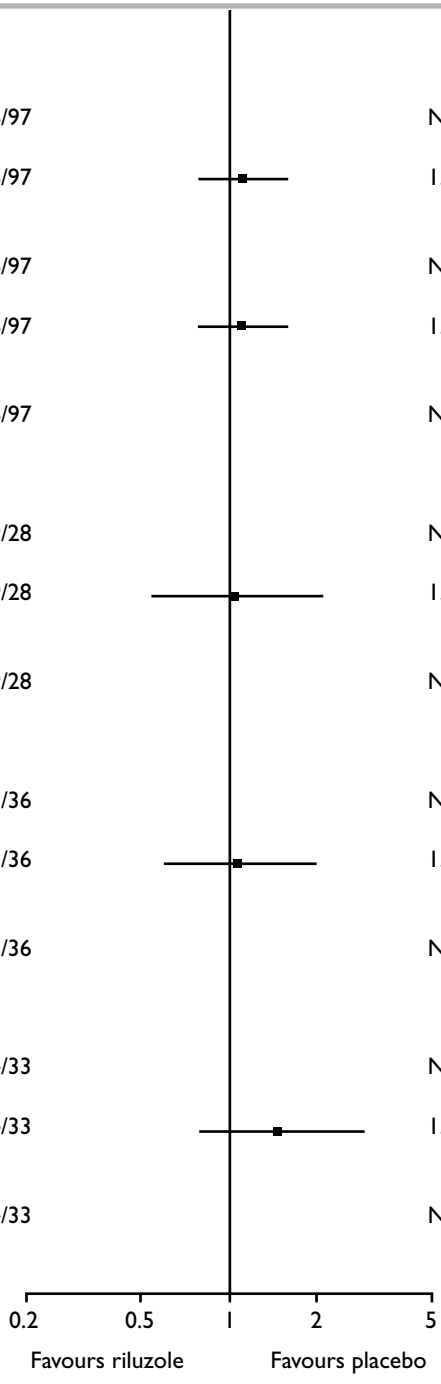


FIGURE 11 *Meininger and colleagues*[44]

Study	Riluzole Events/total	Placebo Events/total	HR with 95% CI	HR (95% CI)	*p*	O-E	V
All patients							
Unadjusted							
Reported	71/98	66/97		Not estimable	–	–	–
Estimated*	71/98	66/97		1.13 (0.78 to 1.64)	0.503	3.55	28.20
Stratified							
Reported	71/98	66/97		Not estimable	–	–	–
Estimated*	71/98	66/97		1.14 (0.78 to 1.00)	0.502	3.04	27.80
Adjusted							
Reported	71/98	66/97		Not estimable	–	–	–
Bulbar site of onset only							
Unadjusted							
Reported	20/28	19/28		Not estimable	0.529	–	–
Estimated*	20/28	19/28		1.05 (0.53 to 2.09)	0.891	0.39	8.08
Adjusted							
Reported	20/28	19/28		Not estimable	–	–	–
Limb site of onset (mild) only							
Unadjusted							
Reported	27/42	23/36		Not estimable	0.563	–	–
Estimated*	27/42	23/36		1.07 (0.58 to 1.97)	0.821	0.73	10.42
Adjusted							
Reported	27/42	23/36		Not estimable	–	–	–
Limb site of onset (severe) only							
Unadjusted							
Reported	24/28	24/33		Not estimable	0.884	–	–
Estimated*	24/28	24/33		1.48 (0.76 to 2.87)	0.247	3.43	8.76
Adjusted							
Reported	24/28	24/33		Not estimable	–	–	–



* *Data not directly reported; results available using summary data from Kaplan–Meier survival curves only*

FIGURE 12 *Yanagisawa and colleagues*[45]

TABLE 18 *Covariates included in the Cox regression models for each trial*

Covariates	Bensimon *et al.*[42]	Lacomblez *et al.*[43]	Meininger *et al.*[44]	Yanagisawa *et al.*[45]
Stratified by site	Yes	Yes	Yes	?
Age	Yes	Yes	Yes	Not stated
VC	Yes	Yes	Yes	Not stated
Duration of disease	Yes	Yes	Yes	Not stated
Bulbar function	Yes	No	No	Not stated
Stiffness scale	Yes	Yes	Yes	Not stated
Tiredness scale	Yes	Yes	Yes	Not stated
Bulbar signs	No	Yes	No	Not stated
Weight	No	Yes	No	Not stated
Muscle testing	No	Yes	Yes	Not stated
CGI severity	No	Yes	No	Not stated
Country grouping	No	Yes	No	Not stated
VAS fasciculations	No	No	Yes	Not stated
Heart rate	No	No	Yes	Not stated

CGI, clinical global impression

Appendix 9

Dosages used in Lacomblez trial

The Lacomblez trial used three different dosages of riluzole (50, 100 and 200 mg). The results for each of these arms are summarised in *Figure 10* (see appendix 8). There was no indication of any difference in effectiveness between these different dosage levels; a much larger trial would be required in order to detect any modest trend in outcome due to the dosage used.

However, the authors of this trial did claim to have found a positive relationship between dose and outcome, but it is not clear that this was an appropriate interpretation of the model they used. The claim was based on fitting 'log-dose' in the Cox proportional hazards model and replacing the undefined log of zero (placebo) with zero (the log of 1). No clear rationale was given by the authors for using log-dose instead of 'dose' in the model. This model is illustrated graphically in *Figure 13*. Note that the CIs for each of the point estimates shown in the figure extend above and below the area of the plot for all doses.

The slope of the 'best straight line' between these points, indicated in the figure, is the estimated change in log HR associated with a unit increase in the log of the dose. Lacomblez and colleagues[43] reported this coefficient as significant, with a HR of 0.95 (95% CI, 0.91 to 0.99; $p = 0.04$). They appear to interpret this as evidence of a dose–outcome relationship. However, the significance of the slope was due to the presence of a drug effect, not the existence of a dose–response relationship. Even if the estimated HRs at each dose level were identical then this analysis would find a significant slope, as long as the common HR was large enough compared to the error in the model (see *Figure 13b*). The log transformation exaggerates the significance of the slope in both models (by altering the position of the observations relative to each other and to placebo on the *x*-axis compared to the untransformed values of 0, 50, 100 and 200), but there is little difference between the two alternatives, as can be seen from the figures.

In order to demonstrate a relationship between dose and outcome, it is necessary to show that a model which contains information on the dosage level clearly fits (or 'explains') the data better than one which merely regards active treatment as present or absent (regardless of the dose used). There is no evidence of any trend in outcome by dosage level in the data presented by Lacomblez and colleagues.[43] Estimates for all dosage levels combined from this trial have therefore been used in the main body of this report.

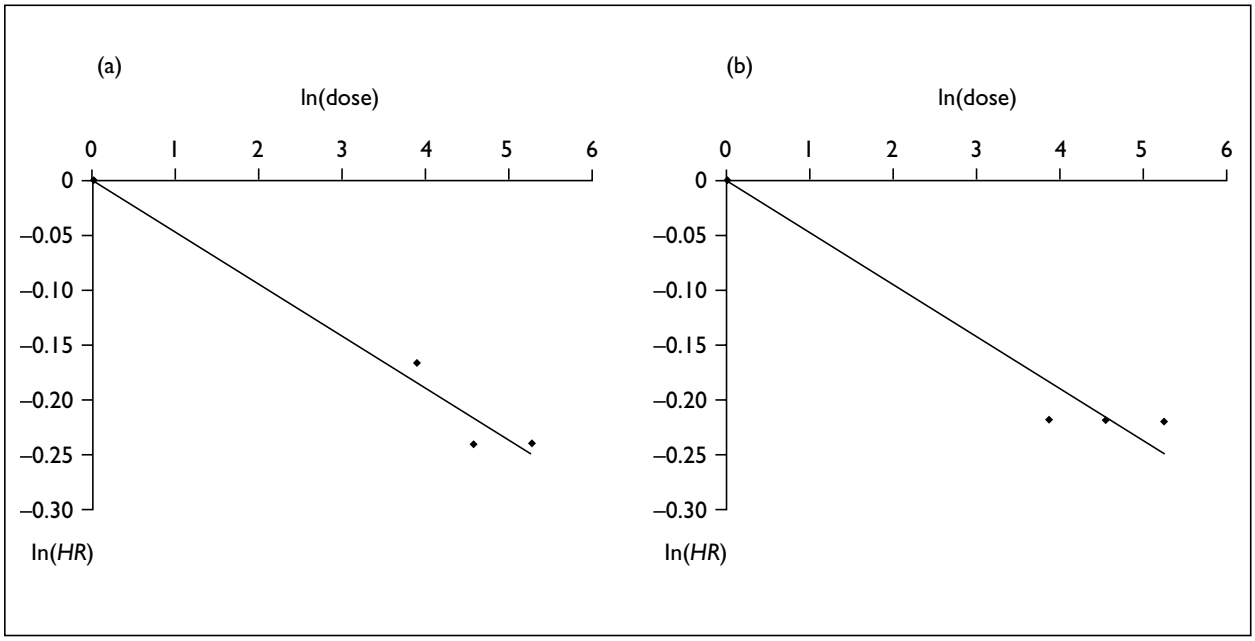


FIGURE 13 *Log-dose in the Cox proportional hazards model. (a) Log-dose analysis in Lacomblez and colleagues, (b) log-dose analysis with same HR at each dose level*

Update

Introduction

This assessment report was commissioned by the HTA programme on behalf of the NICE. The report was submitted in August 2000. Afterwards, the manufacturers of riluzole provided some additional information, which had been requested whilst the report was in preparation. Additional materials were prepared for NICE on the basis of the new information.

New information made available

Three new items were received from the company at different times following submission of the assessment report to NICE:

- some results from an unpublished individual patient data meta-analysis, prepared for the EMEA, including some previously unavailable results from the Yanagisawa trial[45,78]
- long-term (4-year) follow-up for the riluzole 100 mg arm of the Lacomblez trial, previously only published in graphic form in Tavakoli and colleagues[63] (see *Figure 6* in main body of this report)
- inputs for the Markov model used in the Aventis submission to NICE[21] and by Tavakoli and colleagues[63] to produce estimates of the cost-effectiveness of riluzole in MND.

Structure of the update section

Each of the new items of information are outlined and discussed in the following three sections of this update and, as appropriate, put into context with the information presented in the main body of this report. The executive summary given at the beginning of this report reflects the updated information presented here.

Individual patient data meta-analysis

Data made available

The report provided by the company[78] summarises the results of a meta-analysis performed by Rhône-Poulenc Rorer (now part of Aventis Pharma) based on individual patient data from all of the trials identified for this review: Bensimon and colleagues,[42] Lacomblez and colleagues,[43] Meininger and colleagues[44] and Yanagisawa and colleagues.[45] Data on riluzole at 50 and 200 mg dosages from Lacomblez and co-workers were not included. The report provided by the company summarises the endpoint of tracheostomy-free survival and, in addition, gives data on overall survival.[78]

Of particular interest are the results of the Yanagisawa trial, as no numerical results were available from the trial report and thus the results from this trial could not be combined with the others in the original report.

Results of a cluster analysis are also summarised in the report made available to us,[78] although it is not clear why this analysis was performed or how these data might be interpreted.

Results as presented

The results for tracheostomy-free survival are summarised on a plot in the report provided by the company. The numerical results are not provided, but the results of the Yanagisawa trial, estimated from the plot, is a HR of 1.26 (95% CI, 0.83 to 1.90) (in favour of placebo).

Inclusion of the Yanagisawa data, as expected, shifts the results for tracheostomy-free survival towards the null; the estimated HR for riluzole 100 mg daily is 0.89 (95% CI, 0.75 to 1.05) compared to our estimate of 0.83 (95% CI, 0.69 to 0.99) from three of the trials (which included all riluzole doses used in Lacomblez and co-workers). The differences between these results are of no practical importance; the upper limit of the CI is still compatible with little or no benefit. However, the impression of heterogeneity, noted in the original assessment report, is strengthened, with a *p*-value for heterogeneity of 0.09 (compared to 0.39 previously).

Results for overall survival, which have not been reported elsewhere, are similar to those for tracheostomy-free survival, with a pooled HR of 0.88 (95% CI, 0.73 to 1.05) with a *p*-value for heterogeneity of 0.06.

Results obtained using the Cox proportional hazards model are also summarised, and these do not substantially alter the conclusions. For

tracheostomy-free survival, the adjusted estimates were 0.81 (95% CI, 0.68 to 0.96) and 0.80 (95% CI, 0.66 to 0.96). Some missing data were imputed for these analyses:[78]

> "In [Meininger and co-workers], the respiratory function was not assessable at baseline for several patients, the minimum value observed among other patients of [Meininger and co-workers] were used in the Cox modelling for VC [(vital capacity)] and FEV_1 [(forced expiratory volume in 1 second)] ratios. For the other missing data, the mean (or the mode for categorical data) in the stratum within each study was used."

It is not possible to assess what influence this may have had on the adjusted estimates.

Results including data on 50 and 200 mg daily of riluzole

As noted in the main body of this report, there is no evidence of a dose–response effect from the trial by Lacomblez and co-workers,[43] the only trial to have compared different doses of riluzole (see appendices 8 and 9 of main report). For this reason, we have combined data for all doses throughout this report in order to obtain more reliable estimates of the treatment effect. We have repeated the analysis presented in the company meta-analysis but including the 50 and 200 mg data from Lacomblez and co-workers.[43] The results are very similar, with an estimated HR of 0.88 (95% CI, 0.75 to 1.02) and a *p*-value for heterogeneity of 0.09.

The higher dose of riluzole of 200 mg daily (100 mg twice a day) is not recommended by Lacomblez and colleagues[43] because it appears to be no more effective than 100 mg daily, but is associated with greater toxicity. The lower dose of 50 mg daily (25 mg twice a day) is also not recommended, but in this case, due to lesser effectiveness; however, this conclusion appears to be based on an error (see appendix 9 of the main report). The evidence from Lacomblez and co-workers[43] is too weak to prove that 25 and 50 mg twice a day are equally effective, but there is no evidence from this trial that the lower dose differs in effectiveness.

In the main body of this report, we consider 25 mg twice a day (50 mg daily) in the sensitivity analysis for cost-effectiveness. As no 25 mg formulation is available, the simplistic (and most optimistic) assumption was made that this would be half the cost of the 50 mg formulation. However, it is worth noting here that the question of dose is not merely one of financial cost. The toxic side-effects reported by Lacomblez and colleagues[43] appear to be dose-dependent, with less toxicity associated with 25 mg twice a day compared to 50 mg twice a day. Better evidence regarding the relative benefits and disbenefits to patients of the different doses is required before the optimal dose of riluzole can be determined.

Cluster analysis

Results of a cluster analysis are also summarised.[78]

> "The purpose of this analysis was to classify patients into groups or clusters based on their baseline characteristics: patients in a given cluster tending to be more similar to each other, and patients in different clusters tending to be dissimilar"

The 'kth nearest neighbour' clustering method was used to define two groups of patients. Baseline characteristics included in the analysis were age, CGI severity, (prior) disease duration, weight FEV ratio, VC ratio, Norris limb scale, muscle testing score and Norris bulbar scale. The clusters obtained in this way were principally defined by respiratory function (FEV and VC).

There are a number of problems with the application and interpretation of the cluster technique used here, although more detailed information than has been provided would be needed for a full critique. It is worth noting that the most influential variables in forming the clusters were FEV and VC. No mention is made of standardised scores being used in the analysis, and the influential nature of these two variables may thus be simply due to the fact that they have the largest numerical values and will thus dominate the analysis regardless of any underlying structure. Furthermore, it is noted in the report[78] that respiratory function was not assessable in large numbers of patients in Meininger and colleagues[44] and that, for analysis, these patients were assigned the minimum values of FEV and VC observed for other patients in the study. This will clearly lead to some spurious 'clustering' based on these variables and, given the importance of these variables in the procedure, would distort the cluster assignment. The results of the cluster analysis and the survival analyses by cluster, as presented, are, therefore, uninterpretable.

Furthermore, it is not clear that an analysis of this type is useful for identifying meaningful subgroups of patients across a large number of variables. Not surprisingly, the two groups identified by the cluster analysis do not differ as much with respect to prognosis as the high- and low-risk groups identified by Lacomblez and co-workers[43] and Yanagisawa and colleagues[45]

using prognostic indices derived from the Cox model. The EMEA were provided with a survival analysis of high- and low-risk groups defined in this way, and noted that benefit appeared to be confined to the high-risk group;[57] we have not been provided with the results of this analysis and thus cannot comment on the validity of this conjecture. It is worth noting, however, that the prognostic index was constructed using data from the largely prevalent population recruited to these trials, and so it is doubtful whether such an analysis could be of any value in determining which, if any, subgroups of the newly-diagnosed population might benefit most from treatment.

Implications of the new data

The results for tracheostomy-free survival using full data from all four trials do not differ markedly from the results we obtained using data from only three of the trials; there is still weak evidence of a small difference in tracheostomy-free survival favouring riluzole. However, the newly available results of the fourth trial, by Yanagisawa and colleagues, are somewhat in favour of placebo and inclusion of these data substantially increases the impression of heterogeneity between these trials. Whilst the trial by Meininger and colleagues[44] clearly recruited a very different patient population from the other three trials, the patient characteristics in the other trials appear very similar with the only clear difference being European versus Japanese settings.

There is no clear explanation for the heterogeneity in the results of these trials and the pooled estimate should therefore be treated with some caution. If the apparent heterogeneity is not due to chance but rather due to differences between the trials, then we cannot assess the 'true' extent of any benefit of riluzole without understanding why these results differ. If, on the other hand, the apparent heterogeneity is due to chance, then the pooled estimate given here is the most reliable estimate currently available.

The economic evaluation of riluzole presented in the health economics results section of the main report employed the most favourable scenario for riluzole, that is, the results of the trials by Bensimon and colleagues[42] and Lacomblez and co-workers[43] combined. This is still the most favourable scenario for riluzole. Inclusion of the data from the trial by Yanagisawa and colleagues[45] would clearly not improve the cost-effectiveness of riluzole and would have limited impact on the range of estimates produced by the sensitivity analyses presented in the original assessment report.

Long-term (4-year) follow-up from Lacomblez and colleagues[43]

Data made available

The new data received from the company relate to 4-year follow-up for tracheostomy-free survival for patients in the riluzole 100 mg daily arm only of the Lacomblez trial.[43] As placebo patients were all offered riluzole at the end of the trial, similar longer-term follow-up data were not provided for this group. Data were also not provided for patients in the other riluzole arms (50 and 200 mg daily) of the trial.

Further analyses

No survival data (from any trial) beyond 18–21 months were available to the review team in preparing the original report. This lack of data was a particular problem for the economic analysis, which identified the survival gain parameter as the key driver of the cost-effectiveness result. Extrapolation beyond the observed survival was undertaken using alternative approaches. The cost-effectiveness results varied widely when alternative extrapolation models were used. A conclusion of the economic analysis (health economics results section of the main report) was that "further research is required to improve on the extrapolation process in this particular case. This might be achieved by using longer-term follow-up data for the riluzole cohorts of trial patients (all placebo patients were offered the switch to riluzole at the end of trial follow-up) and exploration of data on the natural history of ALS in the absence of riluzole."

The additional data subsequently provided by the company have been used to extend the economic analysis. The revisions to the analysis are detailed below.

1. Survival estimates for riluzole have been obtained from the 4-year follow-up data provided. Note that this 4-year follow-up was only made available for the 236 patients taking riluzole 100 mg daily in the Lacomblez trial.[43] The original analysis used 18-month follow-up data from 794 patients taking any dose of riluzole in two trials, Lacomblez and colleagues and Bensimon and colleagues.[42]
2. Survival estimates for placebo have been taken from 18-month follow-up on the 242 patients on the placebo arm of Lacomblez and colleagues.[43] Longer-term follow-up data for this group are not interpretable as all placebo patients were offered riluzole at the end of the trial. The original analysis used 18-month follow-up data

for the 320 placebo patients from two trials, Lacomblez and co-workers[43] and Bensimon and colleagues.[42]
3. The extrapolation beyond observed survival was undertaken using both Weibull and Gompertz models for both riluzole and placebo groups. The original analysis used the same approach to extrapolation but with 18-month follow-up for both groups.

All other parameter values and assumptions used in the original analysis have been used in this further work.

Results

Table 19 shows the parameter values used in the original and revised analyses. The survival curves resulting from this further analysis are reported in *Figures 14* and *15* (using the Weibull and Gompertz models, respectively). The mean survival for patients in each group was estimated as the area under the survival curve. The results of the revised analyses indicate a larger survival gain for patients on riluzole and a higher cost than originally estimated (see *Table 20*). These results translate into a more attractive cost-effectiveness profile for riluzole, but must be viewed with caution.

Reasons for further caution

Despite the fact that the analysis reported here makes use of longer-term follow-up data, it should be viewed with caution. It would be inappropriate to place any great confidence in the results of the revised (rather than the original) analysis for two reasons:

1. The data used in the analyses reported here are from a single trial (Lacomblez and colleagues[43]) and, for the active drug, include only patients allocated to the riluzole 100 mg arm – all data on patients allocated to either 50 or 200 mg have been ignored. Longer-term follow-up data on such patients have not been provided.
2. We still do not have **comparative** data beyond 18 months. The (unjustified and untestable) assumption made in this further analysis is that longer-term follow-up for placebo patients, if available, would not alter extrapolated survival estimates for this group.

It remains the case that further research is required. In particular, firmer estimates are required of the longer-term survival patterns for patients not treated with riluzole, possibly using data from observational cohort studies of the natural history of ALS where available.

Review of the Markov model used by Tavakoli and colleagues[63]

Data made available

The company provided the review team with a copy of the Markov model that formed the basis

TABLE 19 *Parameters for the original and revised economic analyses. (Data in italics indicate parameters with different values in the revised analysis)*

Parameters	Original analysis	Revised analysis (Weibull model)	Revised analysis (Gompertz model)
Undiscounted survival (months) with riluzole	*21.38*	*26.15*	*25.44*
Undiscounted survival (months) with placebo	*19.67*	*20.03*	*17.98*
Discounted survival (months) with riluzole	*20.85*	*25.35*	*24.68*
Discounted survival (months) with placebo	*19.24*	*19.58*	*17.64*
Proportion of patient withdrawals from riluzole	0.25	0.25	0.25
Riluzole cost per daily dose (£)	10.21	10.21	10.21
Patient monitoring cost per month (£)	17	17	17
Annual care cost – ALS health state I	1237	1237	1237
Annual care cost – ALS health state II	834	834	834
Annual care cost – ALS health state III	1771	1771	1771
Annual care cost – ALS health state IV	3263	3263	3263
Discount rate	6%	6%	6%
Utility – ALS health state I	0.79	0.79	0.79
Utility – ALS health state II	0.67	0.67	0.67
Utility – ALS health state III	0.71	0.71	0.71
Utility – ALS health state IV	0.45	0.45	0.45

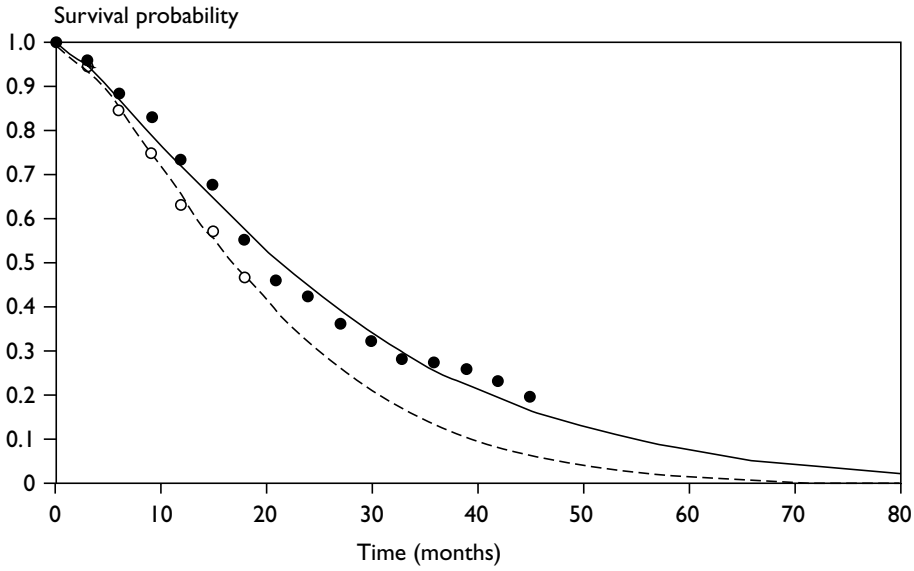


FIGURE 14 *Survival curves with Weibull extrapolation (——, riluzole Weibull; – – –, placebo Weibull; ●, riluzole observed; ○, placebo observed)*

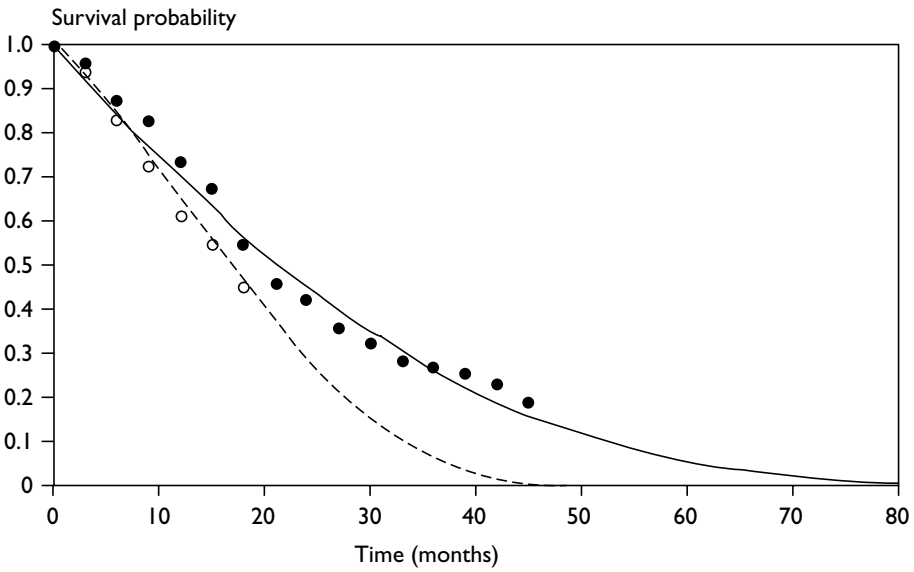


FIGURE 15 *Survival curves with Gompertz extrapolation (——, riluzole Gompertz; – – –, placebo Gompertz; ●, riluzole observed; ○, placebo observed)*

of the economic analysis published by Tavakoli and colleagues[63] and the economic analysis reported in the company's submission to NICE.[21] The model was based on the clinical data from the placebo and riluzole 100 mg daily arms of the trial by Lacomblez and co-workers.[43] The model was created using DATA software[79] and provided to us as electronic DATA files.

Analysis

The purpose of this section of the report is to provide verification of the results of the economic

TABLE 20 *Results of the revised analyses*

Results	Original analysis	Revised analysis (Weibull model)	Revised analysis (Gompertz model)
Lifetime cost of riluzole	£4,841	£5,875	£5,721
Lifetime cost of monitoring	£242	£276	£271
Additional care costs due to survival increase	£112	£401	£489
Life-years gained	0.13	0.48	0.59
QALYs gained	0.09	0.32	0.39
Increase in costs	£5,200	£6,500	£6,500
ICER (cost per life-year)	£39,000	£14,000	£11,000
ICER (cost per QALY)	£58,000	£20,000	£16,500

analysis reported in the Aventis submission to NICE.[21] The model structure is outlined, a simple re-running of the model (as provided) is then described, and finally the results from further re-analyses are presented, where correction is made for a logic error in the model and an alternative approach to extrapolation over time is considered.

Model structure

The structure of the model is shown in *Figure 16* (a modified version of the figure included in the company submission to NICE). The model compared two strategies, labelled 'riluzole' and 'usual care'. The latter refers to the placebo arm of the trial from which the data were drawn. Patients entered the model in one of four states (Mild, Moderate, Severe and Terminal) and, at each (2-month) cycle, could progress from the current state to a more severe state or to death. The model also allowed for some regression to a less severe state (although this was not indicated in the figure provided by Aventis in the NICE submission).

Note that the clinical data on which the model is based is that from the placebo and 100 mg daily arms of Lacomblez and co-workers,[43] which had follow-up visits every 3 months. No reason is given for the choice of a 2-month cycle in this

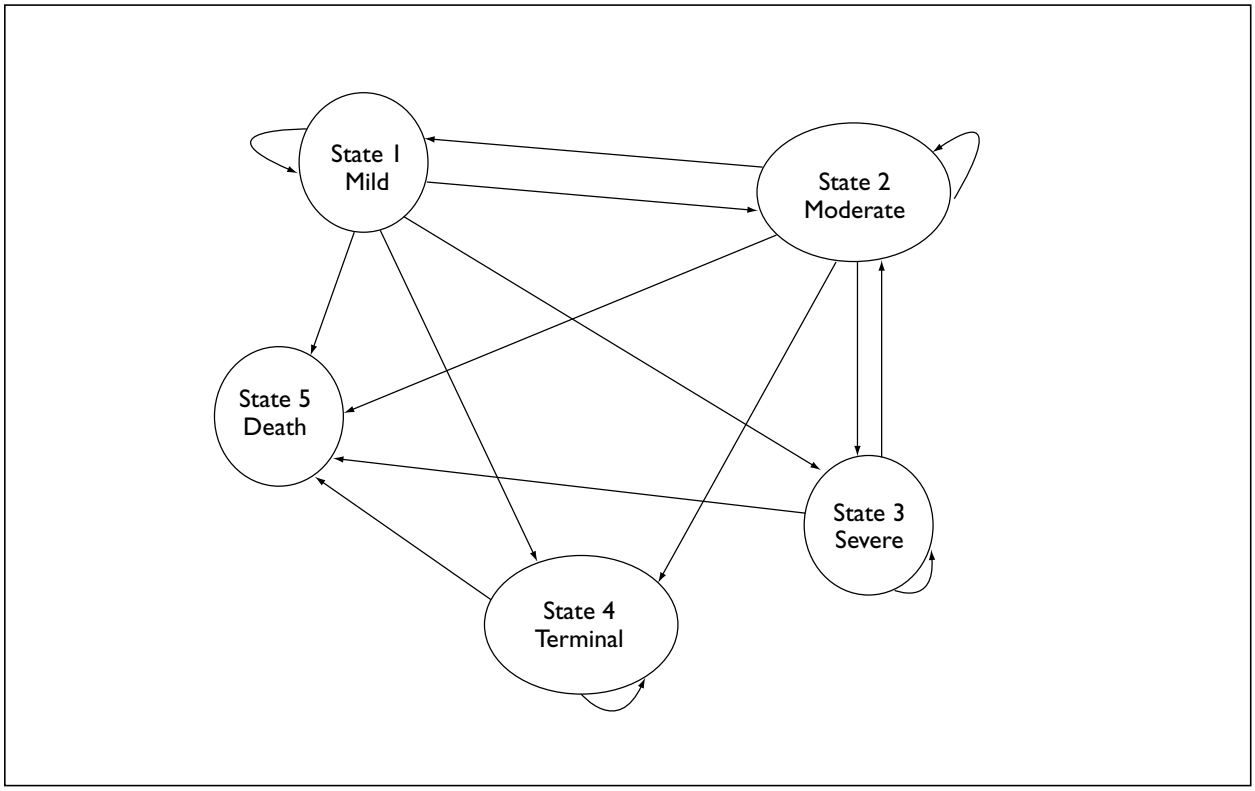


FIGURE 16 *Markov model used in CUA reported in Aventis NICE submission*[21]

model; Tavakoli and colleagues simply note that this was 'indicated by the data'. It is not clear what method was used to obtain 2-monthly transition probabilities from the 3-monthly clinical follow-up.

Replication of the model, as provided

The model has been re-run in order to confirm the results reported in the Aventis NICE submission.

Base-case analysis

The baseline distribution of patients is shown in *Table 21* (these figures are taken from table 2 of Tavakoli and colleagues). Results have been obtained relating to total costs and effectiveness for each branch. The survival curves for the two arms from the re-running of the model were as plotted in *Figure 17*. This is consistent with figure 2 from Tavakoli and colleagues[63] (reproduced as *Figure 6* in the health economics results section of the main report).

Three choices of cost data were used, as shown in *Table 22,* which shows costs per 2-month cycle in each health state. The figures for baseline and maximum costs were obtained directly from the model; they are within a few pence of the results of dividing the annual costs from the Aventis submission by six. As no version of the model with minimum costs was supplied, the minimum costs were calculated from the Aventis submission to NICE.

Future costs were discounted at 6% per year in the usual way, as in Tavakoli and colleagues.[63]

TABLE 21 *Initial distribution of patients in Markov model*

State	Mild	Moderate	Severe	Terminal
Percentage	19.18	67.29	12.57	0.96

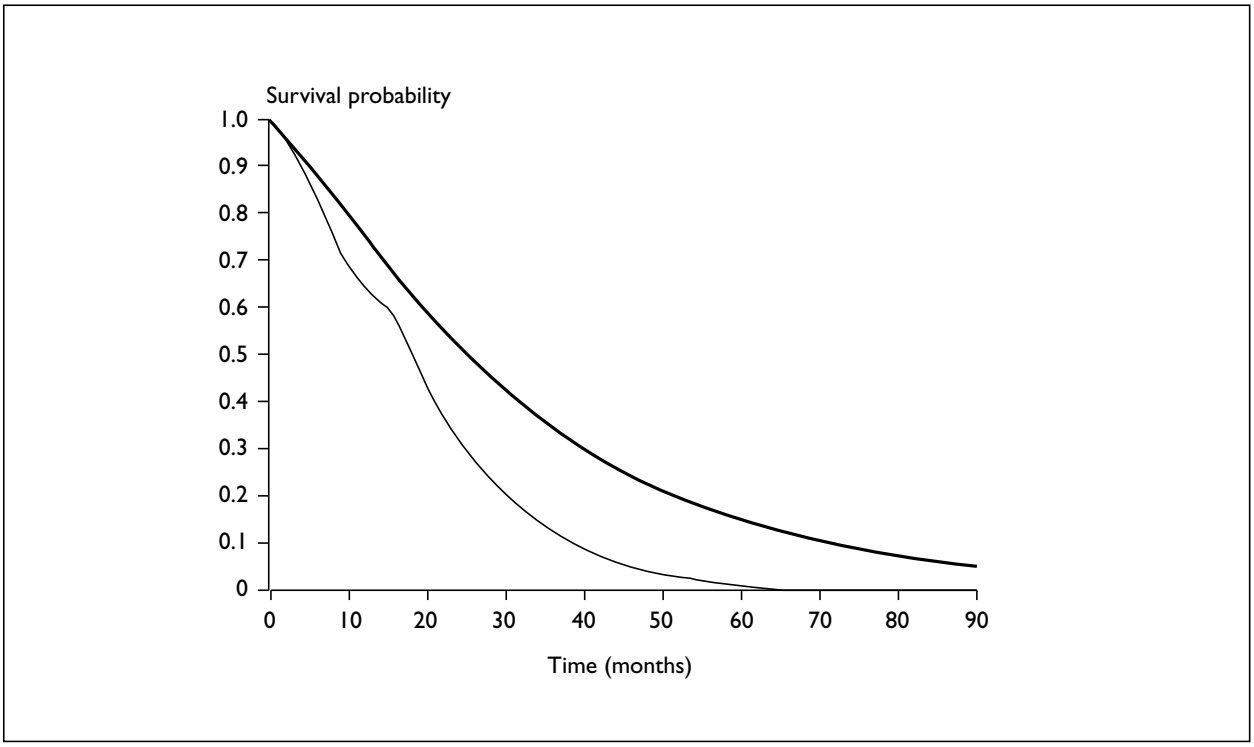


FIGURE 17 *Survival curves from Markov model (——, riluzole; – – –, usual care)*

TABLE 22 *Costs (£) for one cycle in each health state*

	Mild	Moderate	Severe	Terminal
Baseline	204.05	134.22	292.30	538.45
Maximum	223.78	144.71	311.85	1969.85
Minimum	148.17	106.67	229.33	315.83

TABLE 23 *Quality-of-life scores for each health state*

	Mild	Moderate	Severe	Terminal
Mean SG	0.79	0.67	0.71	0.45
Median SG	0.80	0.75	0.78	0.50
Mean VAS	0.74	0.63	0.51	0.37
Median VAS	0.80	0.60	0.50	0.40

Benefits were measured by assigning a quality-of-life score to each state. Scores were obtained from ALS patients using SG and VAS techniques. The relevant figures from the Aventis submission are reproduced in *Table 23*. It should be noted that these were drawn from very small samples (at most 21 patients in any group) and the fact that the severe state is rated higher than the moderate state is compatible with random error. (The SG median score for severe state is given as 0.75 in table 21 of the Aventis NICE submission,[21] but 0.78 in the models; the calculations in this report have assumed 0.78 to be the correct value.)

The base-case version of the model used baseline costs from *Table 23* and undiscounted SG mean quality-of-life scores. In the usual-care arm of the model, the average (discounted) cost per patient was calculated as £2376.72, while the effectiveness measure was 6.666 quality-adjusted 2-month cycles per patient. The corresponding figures for the riluzole arm were £12,025.46 and 11.340, respectively. The QALY gain per patient is:

$$\frac{2}{12} \times (11.340 - 6.666) = 0.779$$

leading to an ICER (measured in £ per QALY) of:

$$\frac{12{,}025.46 - 2376.72}{0.779} = 12.386$$

In the Aventis submission, the figure is given as £12,384 per QALY; the ICERs quoted in the submission are all multiples of six, presumably resulting from rounding of an intermediate answer. The difference is quite unimportant, but the figures in this report were calculated to full accuracy and rounded only at the last step.

Sensitivity analysis

In addition to the base case, eight variations were considered in the sensitivity analysis reported in the Aventis submission. Each variation used the same transition probabilities between states but varied cost and utility values and whether benefits were discounted. The baseline costs were used with median SG utility values and with mean VAS scores, while the minimum and maximum costs were used with the (baseline) mean SG utility scores. The values used are given in *Tables 22* and *23*. In each case, except the mean VAS scores, calculations were made with benefits both undiscounted and discounted. *Table 24* shows our calculations including the 'missing' case. All figures are ICERs in £ per QALY. Our analysis is in agreement with that of Aventis apart from rounding conventions, with one exception, where the figure from the report is given in italics in *Table 24*. Given that the quoted figure is identical to that from another line, it seems likely that this represents a clerical error.

TABLE 24 *Repeating the sensitivity analysis from the Aventis submission*[21]

Costs	Benefits	Benefits discounted?	Our calculations	Aventis submission
Baseline	Mean SG	No	12,386	12,384
Baseline	Mean SG	Yes	15,529	14,160
Baseline	Median SG	No	11,294	11,292
Baseline	Median SG	Yes	14,161	14,160
Baseline	Mean VAS	No	15,175	15,174
Baseline	Mean VAS	Yes	18,978	Not given
Minimum	Mean SG	No	12,165	12,162
Minimum	Mean SG	Yes	15,252	15,252
Maximum	Mean SG	No	11,645	11,646
Maximum	Mean SG	Yes	14,600	14,598

Further re-analysis

Further re-analysis was undertaken for two reasons: first, because an error in the logic of the constructed model has been found, and second, to consider an alternative approach to extrapolation over time.

Error in the logic of the model

Figures 18 and *19* are extracts from the two arms of the model as displayed by DATA.[79] *Figure 18* shows the (correct) logic in transitions from the Terminal state used in the usual-care arm of the model, while *Figure 19* shows an error in the logic used for the riluzole arm. The effect of the error is that riluzole patients who should have remained in the Terminal state from one cycle to another were instead changed to the Severe state, while riluzole patients who should have died from the Terminal state remained alive and in the Terminal state. That is, it was not possible for riluzole patients in the Terminal state to die without first regressing to the Severe state. Thus, the death rate in the riluzole arm is potentially quite seriously underestimated.

We constructed a revised version of the model, adjusting the logic on the riluzole arm to agree with that on the usual-care arm and to be consistent with *Figure 16*. Running this gave a corrected survival curve. *Figure 20* shows the corrected survival curve ('riluzole corrected') alongside the original version ('riluzole original'). The difference can be clearly seen in the diagram. The ICER calculations were repeated using the corrected model, which gave a revised base-case ICER of £20,906 per QALY. Our re-analysis also included other scenarios, so that each combination of costs was combined with each set of utility values, both undiscounted and discounted. The results appear in *Table 25,* which gives a comparison between the corrected and original Aventis version of the model.

How the transition probabilities vary with time

The model as reported in the Aventis NICE submission[21] uses time-dependent Markov transition probabilities. This is managed by use of table files. A typical example of such a file is shown in *Table 26,* which gives the transition

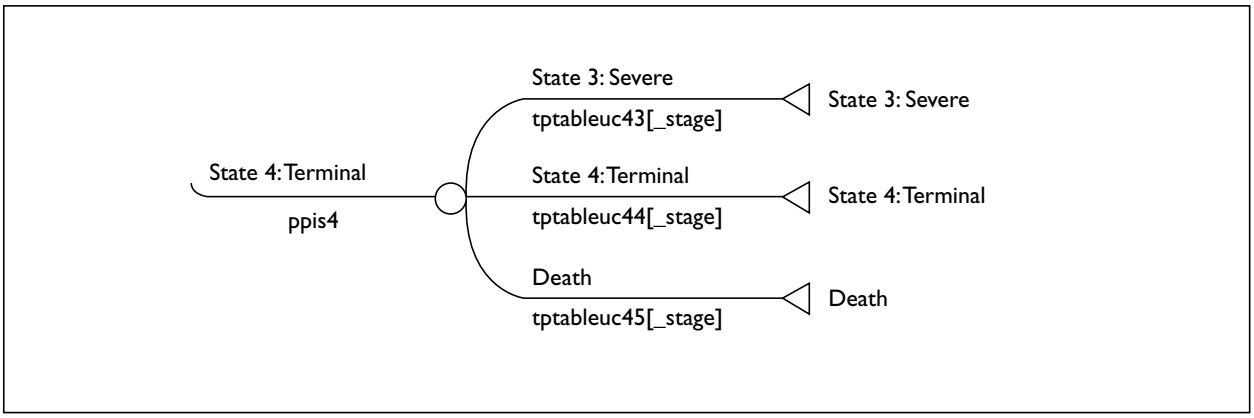


FIGURE 18 *Extract from usual-care arm of model*

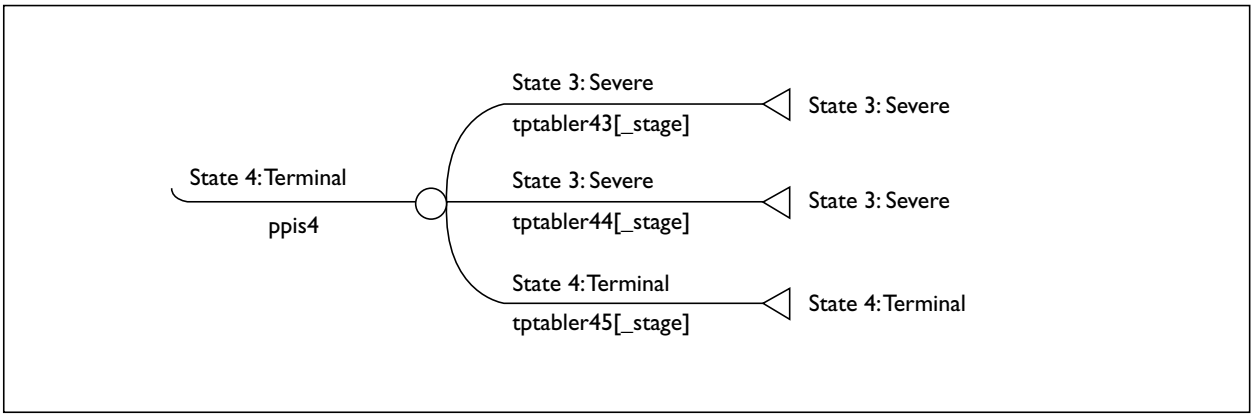


FIGURE 19 *Extract from riluzole arm of model*

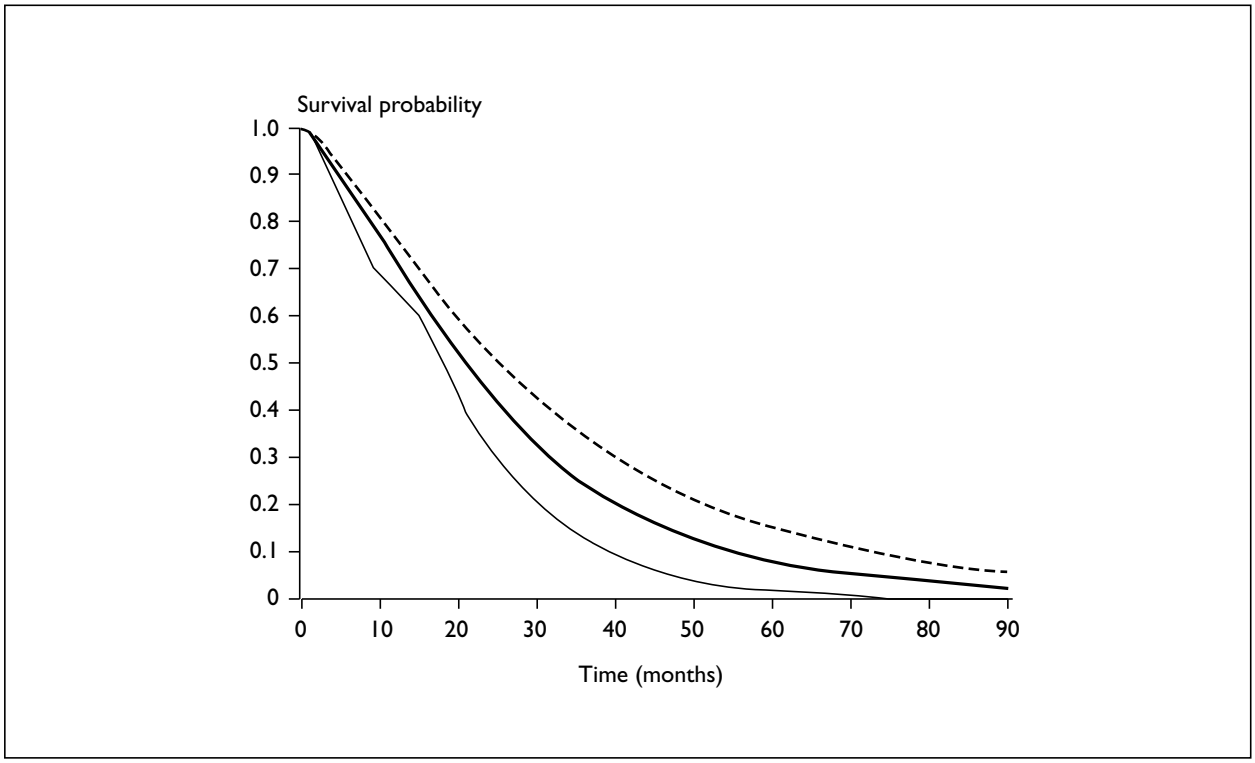


FIGURE 20 *Survival curves from original and corrected models (– – –, riluzole; ——, riluzole corrected; ——, usual care)*

TABLE 25 *Economic analysis of the corrected model*

Costs	Benefits	Benefits discounted?	Corrected model	Original Aventis model
Baseline	Mean SG	No	20,906	12,386
Baseline	Mean SG	Yes	25,793	15,529
Baseline	Median SG	No	19,091	11,294
Baseline	Median SG	Yes	23,554	14,161
Baseline	Mean VAS	No	23,398	15,175
Baseline	Mean VAS	Yes	28,672	18,978
Maximum	Mean SG	No	21,371	11,645
Maximum	Mean SG	Yes	26,367	14,600
Maximum	Median SG	No	19,516	10,618
Maximum	Median SG	Yes	24,077	13,313
Maximum	Mean VAS	No	23,918	14,267
Maximum	Mean VAS	Yes	29,310	17,842
Minimum	Mean SG	No	20,586	12,165
Minimum	Mean SG	Yes	25,399	15,252
Minimum	Median SG	No	18,799	11,093
Minimum	Median SG	Yes	23,194	13,909
Minimum	Mean VAS	No	23,040	14,904
Minimum	Mean VAS	Yes	28,234	18,639

probability from the Terminal state to Death in each cycle of the riluzole arm. The values in *Table 26* are used for the first nine cycles (the first cycle being numbered 0). After this, the last transition probability is simply repeated for all remaining cycles.

TABLE 26 *Transition probabilities from Terminal to Death under riluzole*

Cycle	Transition probability
0	0.0000
1	0.0625
2	0.3333
3	0.1177
4	0.0930
5	0.3334
6	0.1579
7	0.1562
8	0.2692
Average	**0.1692**

It is not at all obvious that merely repeating the transition probability from the last measured cycle for the rest of time is an appropriate way of carrying probabilities forward. This is effectively giving all the weight to the data relating to the last cycle, and zero weight to earlier cycles. The sample size at the end of the trial period was only about half of that at the beginning because of attrition due to death and loss to follow-up. Thus, in the model used above, survival is extrapolated for about 7 years based on transition probabilities estimated from what happened to just half of the patients in the last 2 months of the trial.

An alternative would be to give equal weighting to all of the observed data. This involves using the average probability of each transition during the first nine cycles. Strictly, this average should itself be weighted to take into account different numbers in the various states through the nine cycles. In the absence of the necessary data, we have simply used the arithmetic mean of the nine probabilities in each case. For example, we have used a fixed probability of 0.1692 for transition from Terminal state to Death in the riluzole arm in the later cycles rather than the fixed probability of 0.2692 used in the Aventis report.

It could be argued that the last set of transition probabilities provides a better prediction of later (unobserved) survival, but this approach is only tenable if the estimates are obtained from a very large data set such that uncertainty in the estimates can be ignored. Note that the approach we have taken here, using a simple average, does give greater weight to transition probabilities in later cycles, as these estimates are not penalised for the smaller sample sizes involved at later timepoints.

The changes were implemented by adding an extra line to each of the table files, giving the average as applying to cycle 9 and hence to subsequent cycles. The new table files are reproduced in update appendix 1. These changes were made to the corrected model as described above. The new version will be referred to as the 'alternative model'. *Figures 21* and *22* show the resulting survival curves. As can be seen, the alternative assumption has very little effect on the survival in the riluzole arm of the model, but makes an appreciable difference to the usual-care arm. The economic effect of the alternative assumption is to change the base-case ICER to £31,546 per QALY. This is shown in *Table 27,* which has an extra column added to the results shown in *Table 25.*

Conclusion

While a Markov model with time-dependent transition probabilities is, in principle, a reasonable choice for analysis of the effect of riluzole in the treatment of ALS, it is important that the limitations of such a model are fully addressed. We have identified a number of errors (mostly minor, but one serious) in the description and analysis of the model supplied to us.[21,63] We have also identified a reservation about the choice of time-dependent probabilities beyond the period of data-collection. While we do not claim that our alternative approach to the extrapolation over time is necessarily the best, we believe that our choice is a reasonable alternative given the limited data made available to us.

In the original report, it was noted that the sensitivity analysis carried out in the Aventis submission was very limited. In particular, nothing affecting survival was varied as part of the reported sensitivity analysis. Survival gain was the key parameter driving the analysis of cost-effectiveness presented in the health economics results section of the main report. The re-analysis of the Markov model presented in this update section considers one alternative estimate of

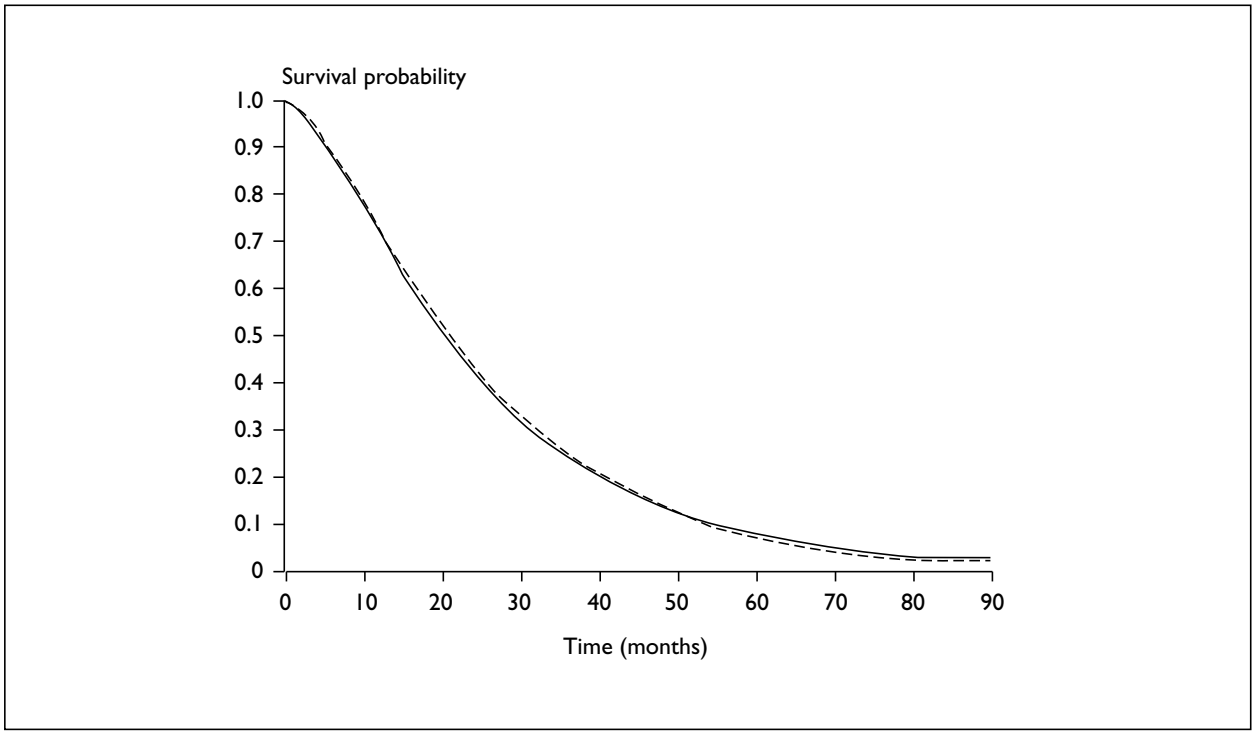


FIGURE 21 *Comparison of survival curves under riluzole (——, corrected model; – – –, alternative model)*

survival pattern, and confirms that the results are sensitive to variation in parameters that influence survival. With access to the raw data, further sensitivity analysis relating to extrapolation of survival could be performed using alternative means of estimating transition probabilities, for example using a 3-month cycle in line with the clinical data collection interval.

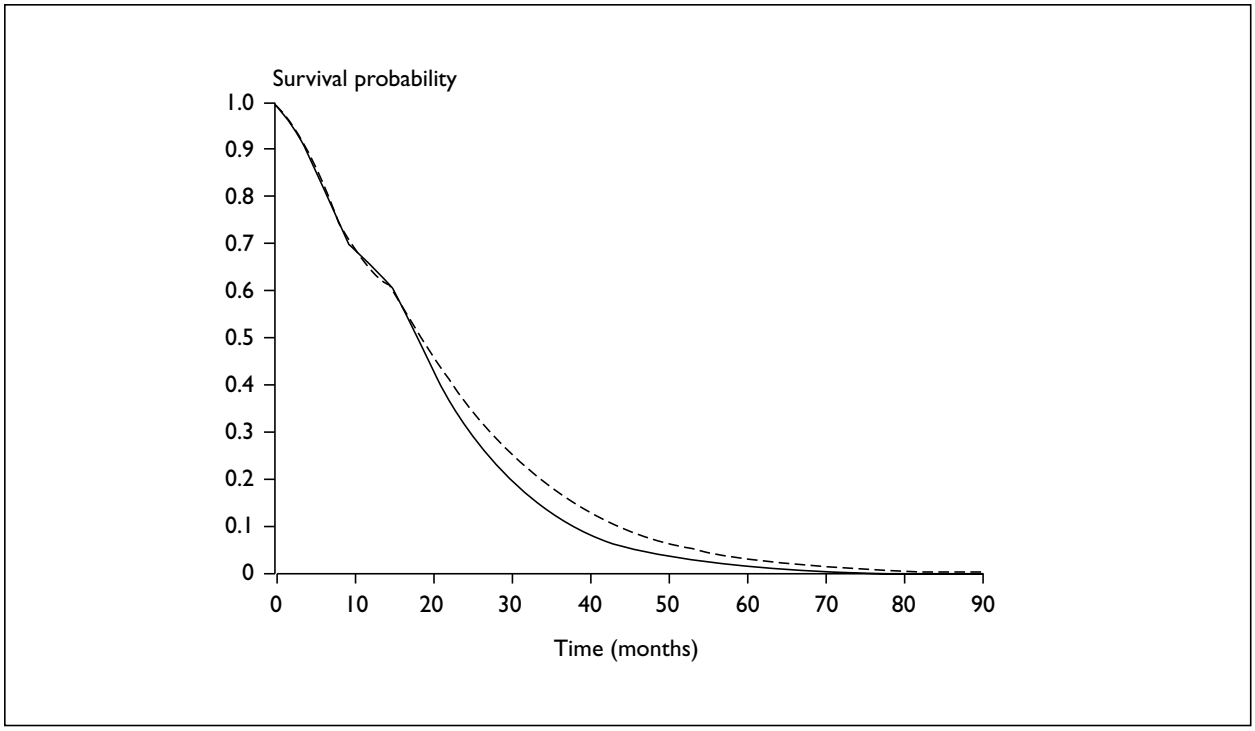


FIGURE 22 *Comparison of survival curves under usual care (——, corrected model; – – –, alternative model)*

TABLE 27 *Economic analysis of the revised model*

Costs	Benefits	Benefits discounted?	Alternative model	Corrected model	Original Aventis model
Baseline	Mean SG	No	31,546	20,906	12,386
Baseline	Mean SG	Yes	38,070	25,793	15,529
Baseline	Median SG	No	28,642	19,091	11,294
Baseline	Median SG	Yes	34,562	23,554	14,161
Baseline	Mean VAS	No	35,411	23,398	15,175
Baseline	Mean VAS	Yes	42,394	28,672	18,978
Maximum	Mean SG	No	32,405	21,371	11,645
Maximum	Mean SG	Yes	39,106	26,367	14,600
Maximum	Median SG	No	29,422	19,516	10,618
Maximum	Median SG	Yes	35,503	24,077	13,313
Maximum	Mean VAS	No	36,375	23,918	14,267
Maximum	Mean VAS	Yes	43,548	29,310	17,842
Minimum	Mean SG	No	31,174	20,586	12,165
Minimum	Mean SG	Yes	37,621	25,399	15,252
Minimum	Median SG	No	28,304	18,799	11,093
Minimum	Median SG	Yes	34,155	23,194	13,909
Minimum	Mean VAS	No	34,993	23,040	14,904
Minimum	Mean VAS	Yes	41,894	28,234	18,639

It should also be noted that this model was based on data from the placebo and riluzole 100 mg daily arms of the Lacomblez trial. More reliable estimates of the effectiveness of riluzole would be obtained by including all of the trial data available.

The main conclusion of this update is that the results quoted in the section above dealing with the replication of the model, as provided, should be viewed with caution.

Update appendix 1

Transition probabilities used in alternative Markov model

Transition cycle	Mild–Mild		Mild–Moderate		Mild–Severe		Mild–Terminal		Mild–Death	
	Usual	Riluzole	Usual	Riluzole	Usual	Riluzole	Usual	Riluzole	Usual	Riluzole
0	0.6744	0.6058	0.3256	0.3796	0.0000	0.0000	0.0000	0.0000	0.0000	0.0146
1	0.6250	0.6373	0.3750	0.3627	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
2	0.6000	0.7500	0.4000	0.2500	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
3	0.6250	0.6667	0.3125	0.3333	0.0000	0.0000	0.0000	0.0000	0.0625	0.0000
4	0.6667	0.7021	0.3333	0.2979	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
5	0.7000	0.7143	0.3000	0.2857	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
6	0.6667	0.8387	0.3333	0.1613	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
7	0.7143	0.8846	0.2857	0.1154	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
8	0.6667	0.7368	0.3333	0.2632	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Average	0.6599	0.7263	0.3332	0.2721	0.0000	0.0000	0.0000	0.0000	0.0069	0.0016

Transition cycle	Moderate–Mild		Moderate–Moderate		Moderate–Severe		Moderate–Terminal		Moderate–Death	
	Usual	Riluzole	Usual	Riluzole	Usual	Riluzole	Usual	Riluzole	Usual	Riluzole
0	0.0191	0.0401	0.7707	0.7848	0.1783	0.1540	0.0000	0.0000	0.0319	0.0211
1	0.0370	0.0096	0.7259	0.8217	0.1852	0.1325	0.0074	0.0096	0.0445	0.0266
2	0.0189	0.0245	0.8113	0.8365	0.1226	0.1144	0.0000	0.0027	0.0472	0.0219
3	0.0543	0.0314	0.7500	0.8145	0.1413	0.1164	0.0000	0.0000	0.0544	0.0377
4	0.0000	0.0073	0.8133	0.7993	0.1467	0.1569	0.0000	0.0036	0.0400	0.0329
5	0.0308	0.0302	0.7692	0.7888	0.2000	0.1638	0.0000	0.0000	0.0000	0.0172
6	0.0189	0.0105	0.8113	0.7749	0.1321	0.1728	0.0000	0.0000	0.0377	0.0418
7	0.0227	0.0069	0.7955	0.8207	0.1364	0.1655	0.0000	0.0000	0.0454	0.0069
8	0.0000	0.0421	0.7037	0.8211	0.2593	0.1263	0.0000	0.0000	0.0370	0.0105
Average	0.0224	0.0225	0.7723	0.8069	0.1669	0.1447	0.0008	0.0018	0.0376	0.0241

Transition cycle	Severe–Mild		Severe–Moderate		Severe–Severe		Severe–Terminal		Severe–Death	
	Usual	Riluzole	Usual	Riluzole	Usual	Riluzole	Usual	Riluzole	Usual	Riluzole
0	–	–	0.0571	0.0127	0.8571	0.7342	0.0571	0.1899	0.0287	0.0632
1	–	–	0.0000	0.0331	0.8103	0.7521	0.0517	0.0744	0.1380	0.1404
2	–	–	0.0145	0.0571	0.7101	0.7143	0.1304	0.1429	0.1450	0.0857
3	–	–	0.0169	0.0368	0.7797	0.6985	0.1017	0.1397	0.1017	0.1250
4	–	–	0.0182	0.0314	0.7636	0.7907	0.0909	0.1163	0.1273	0.0616
5	–	–	0.0189	0.0500	0.7547	0.7286	0.1321	0.0929	0.0943	0.1285
6	–	–	0.0600	0.0534	0.7400	0.7863	0.1400	0.0534	0.0600	0.1069
7	–	–	0.0256	0.0360	0.7179	0.7568	0.2308	0.0811	0.0257	0.1261
8	–	–	0.0417	0.0250	0.7500	0.7750	0.0833	0.0875	0.1250	0.1125
Average	–	–	0.0281	0.0373	0.7648	0.7485	0.1131	0.1087	0.0940	0.1055

Transition cycle	Terminal–Mild		Terminal–Moderate		Terminal–Severe		Terminal–Terminal		Terminal–Death	
	Usual	Riluzole	Usual	Riluzole	Usual	Riluzole	Usual	Riluzole	Usual	Riluzole
0	–	–	–	–	0.0000	0.0000	1.0000	1.0000	0.0000	0.0000
1	–	–	–	–	0.0000	0.0625	0.8000	0.8750	0.2000	0.0625
2	–	–	–	–	0.0000	0.0000	0.7143	0.6667	0.2857	0.3333
3	–	–	–	–	0.0000	0.0588	0.6923	0.8235	0.3077	0.1177
4	–	–	–	–	0.0000	0.0465	0.6923	0.8605	0.3077	0.0930
5	–	–	–	–	0.0714	0.0208	0.6429	0.6458	0.2857	0.3334
6	–	–	–	–	0.0000	0.0789	0.9333	0.7632	0.0667	0.1579
7	–	–	–	–	0.0625	0.0625	0.8125	0.7813	0.1250	0.1562
8	–	–	–	–	0.0000	0.0385	0.6875	0.6923	0.3125	0.2692
Average	–	–	–	–	0.0149	0.0409	0.7750	0.7898	0.2101	0.1692

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We look forward to hearing from you.

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