# The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease - An update

Stirling Bryan, Pelham Barton, Amanda Burls

## Introduction

In the report by the West Midlands Development and Evaluation Service report "The clinical and cost-effectiveness of riluzole for motor neurone disease" submitted to NICE[1] it was noted that:

"Further unpublished survival data have been produced for the study by Lacomblez *et al* (1996)"

and that

"Despite our contacting the authors and a request to the manufacturer via NICE, these missing data have not been made available at the time this report was completed."

The consequence of this was that no survival data beyond 18 months were available to the review team.

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 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."

Since the submission of the report, new data from the trial reported in Lacomblez *et al* (1996)[2] has been received from Aventis. These data relate to patient survival or tracheostomy (i.e. the main end-point used in the trial) for a follow-up period of 48 months for patients in the riluzole 100mg arm of the trial. Since placebo patients were all offered riluzole at the end of the trial follow-up (i.e. 18 months), similar longer-term follow-up data are not available for placebo patients. However, such data should be available for patients in the other riluzole arms (50mg and 200mg) but these have not been provided.

## Further analyses

These additional data have been used to extend the economic analysis. The revisions to the analysis are detailed below.

1. Survival estimates for riluzole have been taken from a single trial (Lacomblez *et al*), using only data relating to a 100mg dose, but including follow-up data through to 48 months. Whilst the original analysis used data from two trials (Lacomblez *et al* and Bensimon *et al*[3]) and for all doses of riluzole, the follow-up was limited to 18 months.

2. Survival estimates for placebo have been taken from a single trial (Lacomblez *et al*), using only 18 month follow-up data – longer-term follow-up data are not available since all placebo patients were offered riluzole at the trial end. The original analysis used 18 month follow-up data for placebo patients from two trials (Lacomblez *et al* and Bensimon *et al*).

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 although with fewer observed data points for the riluzole group.

All other parameter values and assumptions used in the original analysis have been used in this further work. Table 1 below shows the parameter values used in the original and revised analyses.

**Table 1 – Parameters for the original and revised economic analyses**

| 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 I | 0.67 | 0.67 | 0.67 |
| Utility – ALS health state I | 0.71 | 0.71 | 0.71 |
| Utility – ALS health state I | 0.45 | 0.45 | 0.45 |

Note: shading indicates parameters with different values in the revised analysis

The survival curves resulting from this further analysis are reported in Figures 1 and 2 (using the Weibull and Gompertz models respectively). The mean survival for patients in each group was estimated as the area under the survival curve.

**Figure 1 – Survival curves with Weibull extrapolation**

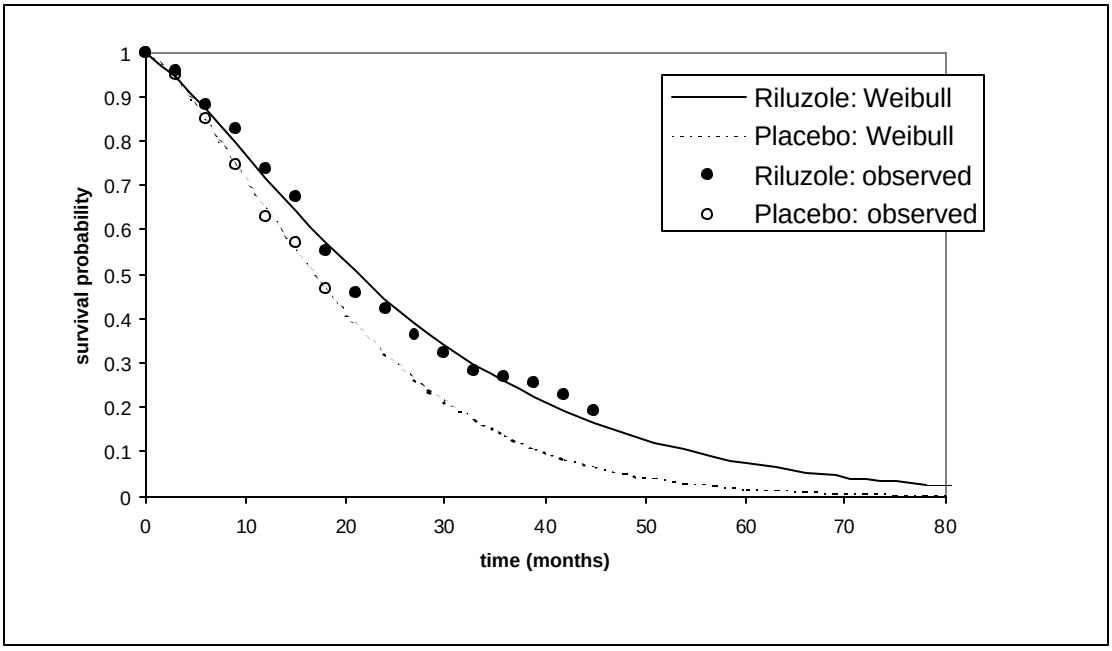
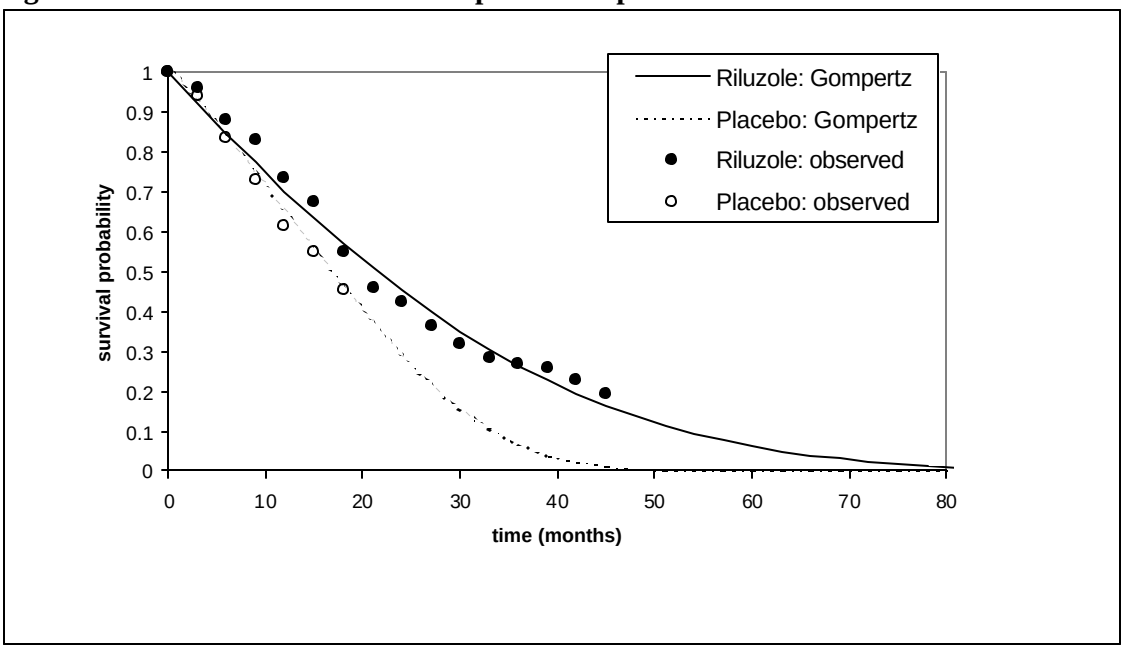



**Figure 2 – Survival curves with Gompertz extrapolation**




The results of the revised analyses are reported in Table 2.

**Table 2 – 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 quality-adjusted life-year) | £58,000 | £20,000 | £16,500 |

The results of this revised analysis indicate a larger survival gain for patients on riluzole and a higher cost than originally estimated. These results translate into a more attractive cost-effectiveness profile for riluzole.

## 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 some caution. It would inappropriate to place a great deal more 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 *et al*) and for the active drug include only patients allocated to the riluzole 100mg arm – all data on patients allocated to either 50mg or 200mg 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 assumption made in this further analysis is that patients allocated to placebo do not follow a similar path, beyond 18 months, to riluzole patients. It remains the case that further research is required. In particular firmer estimates are required of the longer-term survival for patients in the absence of riluzole, possibly using data from observational cohort studies of the natural history of ALS, where available.

Reference List

1. Stewart A, Sandercock J, Bryan S, Hyde C, Fry-Smith A, Burls A. The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease. Submission to NICE, 2000.

2. Lacomblez L, Bensimon G, Leigh PN et al. Dose-ranging study of riluzole in amyotrophic lateral sclerosis. *Lancet* 1996;347(9013):1425-31.

3. Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. *N Eng J Medicine* 1994;330(9):585-91.