Supplementary Analyses of various historical placebo controls

Control Groups

We used our database of placebo patients from previous clinical trials as controls for lithium patients in this study. Our database contains repeated ALSFRS-R scores from six completed clinical trials: NEALS creatine, NEALS celebrex, NEALS lithium, Novartis TCH436, QALS trial of CoQ10, and WALS minocycline. Table 1 summarizes numbers of placebo patients and their characteristics.

The trials in Table 1 were conducted over a 9 year period and showed no evidence of change in FRS-R slope (our primary outcome measure) over time. Patient entry characteristics were similar except for restricted entry for the TCH346 and minocycline trials that enrolled patients with FVC minimum of 75% and symptom duration 3 years or less. Both of these trials had a 4 month lead-in where none of the patients received the study drug and were then randomized. In the minocycline trial 45 patients dropped out during the lead-in but their data were included. In the TCH346 trial we only have data for those randomized at 4 months. This could explain the lower estimated slope for TCH346 placebo since those with rapidly declining FRS-R scores may have been more likely to drop out prior to randomization. Slope comparisons in Table 1 are based on fitting a linear mixed effect model to each dataset independently and are based on 6 months followup. This was done to make the slopes comparable since two of the studies had only 6 months of followup for most patients.

We found no significant differences in FRS-R slopes among the different placebo groups ($p=0.53$, based on comparing chi-squares from separate fits with that from a pooled fit). However, previous work using this database showed that slopes are influenced by initial FVC and symptom duration. Thus, our primary comparison control consisted of placebo patients from the minocycline trial since the lithium phase II trial had the same entry criteria and was conducted at many of the same sites as the minocycline trial.

Results of Lithium vs Placebo Comparisons

We were fortunate to obtain data from a recent placebo-controlled clinical trial of lithium conducted by the NEALS group [1]. This trial was stopped after the first interim analysis for futility. Patient characteristics and ALSFRS-R slopes over the first six months of followup for the two arms of this trial are included in Table 1. It is interesting to note that ALSFRS-R slopes for the NEALS lithium placebo arm is similar to those from other placebo groups and that the slopes for the two lithium treated groups are similar ($p=0.66$ for testing slope difference between the two lithium groups after fitting with a linear mixed effect model).

Results of comparing the WALS lithium patients with different placebo groups are summarized in Table 2 and are based on fitting all follow-up data (not just the first 6 months as in Table 1). The estimates for the comparisons shown in Table 2 are based on

a model with an additional quadratic term for follow-up time since slopes increase over time and the quadratic term for time becomes significant when follow-up is longer than 6 months. Thus slopes reported in Table 2 are not directly comparable to those in Table 1.

Since we found no statistical difference between the ALSFRS-R slopes of WALS and NEALS lithium groups, their data were combined and compared to the pooled placebo patients from all studies. The results are in agreement with those using the WALS data alone (line 4 vs line 2 of Table 2).

We also compared results from the WALS lithium study with each placebo group from our database. We matched patients' entry criteria to that of the WALS minocycline and lithium trials (Table 3). These comparisons suggest that rates of decline of ALSFRS-R for lithium-taking patients was worse than those for the subset of comparable placebo patients in each other trial, except for patients in the NEALS creatine trial, where the slope was unusually high compared to the other placebo trial subgroups.

Table e-1: Comparison of Placebo and Lithium Trials Subgroups*

	Placebo							Lithium	
Trial	NEALS creatine	NEALS celebrex	Novartis TCH346	WALS Minocycline[1]	Columbia multicenter CoQ10	NEALS Lithium	All Placebo	NEALS Lithium	WALS Lithium
Years	2000-02	2001-03	2004	2005-07	2005-07	2009	2000-2009	2009	2009
N patients*	45	95	108	249	75	44	616	39	107
Trial duration	6 mos	12 mos	10 mos	13 mos	9 mos	6 mos	6 - 13 mos	6 mos	13 mos
Symptom duration (yrs)	0.6 - 4.8	0.4 - 5.1	0.3 - 3.0	0.2 - 3.8	0.5 - 5.5	0.5 - 3.0	0.2 - 5.5	0.6 - 2.9	0.2 - 3.3
Entry FVC median	82.9	83.5	88.5	91.0	90.0	87.5	89.0	93	91
Entry FVC range	47 - 134	57 - 146	39 - 147	72 - 178	61 - 128	56 - 134	39 - 178	59 - 135	73 - 133
Entry FRS-R median	38	40	40	39	36	37	39	40	38
Entry FRS-R range	18 - 47	22 - 47	26 - 47	23 - 48	27 - 43	24 - 48	18 - 48	27 - 45	18 - 47
Est. FRS-R Slope/mo[2]	-0.98	-1.06	-0.79	-0.94	-0.82	-1.00	-0.89	-1.29	-1.21
Slope 5th, 95th percentile	-2.50 -0.14	-2.49 -0.12	-2.66 +0.03	-2.52 +0.00	-1.75 -0.16	-2.69 +0.25	-2.45 +0.01	-3.90 -0.03	-3.14 -0.24

*Patients with 2 or more assessments

[1]Includes nonrandomized patients

[2]Slopes estimated from linear mixed effects model applied to first 6 months of follow-up; separate estimation for each data subset without reference to other studies.

Table e-2: Lithium comparisons with controls*

					Controls		Lithium	Lithium Effect		
Controls	Restrictions	Total N	N Lith	N Cont	Slope[1]	95% CI	Slope	Slope change	95% CI	p-value
WALS Lithium vs. Mino controls	>1 visit	356	107	249	0.87	0.75-0.99	1.06	0.19	0.01-0.37	0.048
WALS Lithium vs. Mino controls	>1 visit, FVC≥75%, sympdur≤3yrs	337	98	239	0.84	0.73-0.97	1.02	0.17	-0.01-0.36	0.069
WALS Lithium vs. All Placebo	>1 visit, FVC≥75%, sympdur≤3yrs	573	98	475	0.80	0.71-0.88	0.99	0.19	0.03-0.36	0.023
Combined Lithium vs. All Placebo	>1 visit, FVC≥75%, sympdur≤3yrs	605	130	475	0.80	0.71-0.88	0.98	0.18	0.03-0.39	0.022

*Comparisons based on fitting a linear mixed effects model to combined placebo and lithium data.

[1]Slopes are linear component estimates from a linear mixed effects model with an additional quadratic term to model increasing slope over time and are based on 13 months of follow-up. Slopes are shown as positive numbers and are estimated rates of decline per month from the linear mixed effects analysis.

Table e-3: Comparison of ALSFRS-R slope for each placebo historical control with lithium for patients with initial FVC≥75 and symptom duration ≤ 2 yrs.

	Placebo		Lithium (Mean)		Baseline features (means)		
Placebo Grp	N	Slope Mean	Difference*	P-val	FVC	Symptom Duration (yrs)	ALSFRS-R
WALS mino	239	0.92	0.21	0.05	94.4	1.4	38.1
NEALS celb	55	1.23	-0.11	0.50	90.6	1.3	40.9
NEALS crea	25	0.94	0.20	0.35	92.7	1.6	39.3
QALS CoQ10	46	0.87	0.28	0.07	100.0	1.6	36.6
NEALS lithium	31	0.95	0.20	0.35	95.6	1.7	37.9
Combined	396	0.96	0.17	0.10	94.5	1.5	38.4
WALS lithium	98	1.15			95.8	1.5	37.4

*Slope mean plus Difference differs for each study due to estimation of random effects, which differ for each study.

Reference

1. Aggarwal SP, Zinman L, Simpson E, et al. Safety and efficacy of lithium in combination with riluzole for treatment of amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2010;9:481-488.