Table e-1. Eligibility Criteria

Inclusion Criteria

1. El Escorial criteria for familial ALS. These require
    a. The presence of progressive upper and/or lower motor neuron signs in at least one of the four body regions (cranial, cervical, thoracic and lumbosacral)
    b. The absence of another cause for the abnormal neurological signs
    c. A family history of a pathogenic mutation in a gene known to be associated with ALS, such as the *SOD1* gene.
2. Willingness to undergo genetic testing and to learn the results, already know the results of genetic testing or know the results of *SOD1* testing in a family member.
3. Demonstrable mutation in the *SOD1* gene that is reported to be associated with a rapid rate of disease progression (i.e. A4V, A4T, C6F, C6G, V7E, L8Q, G10V, G41S, H43R, H48Q, D90V, G85R, G93A, D101H, D101Y, L106V, I112M, I112T, R115G, L126X, G127Gfs*7, A145T, V148G, V148I) or a history of rapidly progressive disease accompanied by a mutation in the *SOD1* gene possibly associated with rapidly progressive disease (e.g. V14G, E21G, G37R, L38V, D76Y, L84F, L84V, N86S, D90A het, G93R, I104F, I113T, L144F, L144S).
4. Age 18 years or older - male or female.
5. Capable of providing informed consent and complying with trial procedures.
6. Diagnosis within 9 months of the anticipated date of the Baseline visit AND study participants' subjective evaluation that they expect their physical condition to permit travel to the study site for both the Baseline and Month-2 study visits.
7. Women must not be able to become pregnant (e.g. post menopausal for at least one year, surgically sterile, or practicing adequate birth control methods) for the duration of the study. Examples of adequate contraception methods include: oral contraception, depo-progesterone injections, implanted contraception, intrauterine device in place for $\geq$ 3 months, abstinence, or a barrier contraceptive such as a condom with or without spermicide cream or gel, diaphragms or cervical cap with or without spermicide create or gel.
8. Women of childbearing potential must have a negative pregnancy test at screening visit and be non-lactating.
9. Willing to remain on a stable dose of riluzole or to remain off riluzole for the duration of the trial.
10. Identifiable local medical doctor to assist with urgent care of any medical complications that may arise.
11. Absence of any of the exclusion criteria.

Exclusion Criteria

1. History of known sensitivity or intolerability to Arimoclomol or to any other related compound.
2. Exposure to any investigational drug within 30 days of the Screening visit.
3. Prior participation in any protocol involving anti-sense oligonucleotides.
4. Presence of any of the following clinical conditions:
    a. Substance abuse within the past year.
    b. Unstable cardiac, pulmonary, renal, hepatic, endocrine, hematologic, or active infectious disease.
    c. AIDS or AIDS-related complex.
    d. Unstable psychiatric illness defined as psychosis (hallucinations or delusions), or untreated major depression within 90 days of the Screening visit.

    e. Positive pregnancy test at Screening visit.
5. Laboratory values:
    a. Creatinine greater than 1.5
    b. Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) greater than 3.0 times the upper limit of normal
    c. Total bilirubin greater than 1.5 times the upper limit of normal
    d. White blood cell (WBC) count less than 3,500/mm^3
    e. Platelet concentration <100,000/ul
    f. Hematocrit level <33 for female or <35 for male
6. Female patients who are breast-feeding

Table e-2. Vital Sign and Laboratory Abnormalities

Vital Sign / Lab Abnormality	Alert Value	Placebo # Events (Patients)	Arimoclomol # Events (Patients)
Low respiratory rate	< 9 breaths/minute	--	2 (1)
High respiratory rate	> 31 breaths/minute	3 (2)	--
Hypothermia	< 35℃	--	1 (1)
Fever	> 37.8℃	1 (1)	3 (1)
Low systolic blood pressure	< 80 mmHg	--	1 (1)
Low potassium	≤ 3 mmol/l	1 (1)	--
High potassium	≥ 6 mmol/l	1 (1)	--
Low chloride	≤ 90 mmol/l	1 (1)	1 (1)
High glucose	≥ 150 mg/dL	8 (4)	9 (3)
High bilirubin	≥ 2 mg/dL	2 (1)	1 (1)
High ALT	≥ 100 U/L	9 (3)	3 (2)
High AST	≥ 110 U/L	2 (2)	--
Low red blood cell count	≤ 3.3 mil/mm^3	--	1 (1)
High hematocrit	≥ 55%	2 (1)	1 (1)

Table e-3. Additional Efficacy Analyses

These additional analyses were performed at the request of the journal/reviewers. Because they were performed post-hoc and not specified in the original statistical analysis plan, they are included in the online supplement rather than in the body of the manuscript.

Model	Treatment Difference: Mean (95% Confidence Interval)					
	All Patients			A4V Patients Only		
	N	Survival: hazard ratio [d]	ALSFRS-R slope: points/month [e]	N	Survival: hazard ratio [d]	ALSFRS-R slope: points/month [e]
Pre-specified [a]	36	0.77 (0.32-1.80)	0.50 (-0.63, 1.63)	26	0.60 (0.22-1.64)	0.98 (-0.28, 2.24)
Adjust for baseline VC	36	0.80 (0.33-1.89)	0.51 (-0.69, 1.71)	26	0.50 (0.17-1.44)	0.93 (-0.36, 2.22)
Adjust for months since onset, including outliers [b]	34	0.72 (0.29-1.80)	0.47 (-0.84, 1.77)	24	0.45 (0.14-1.58)	0.98 (-0.58, 2.53)
Adjust for months since onset, excluding outliers [b, c]	32	0.69 (0.27-1.77)	0.45 (-0.80, 1.70)	23	0.28 (0.08-1.01)	1.19 (-0.22, 2.59)
Adjust for ΔFRS, including outliers [b]	34	0.56 (0.21-1.45)	0.50 (-0.77, 1.77)	24	0.30 (0.09-1.06)	0.96 (-0.55, 2.47)
Adjust for ΔFRS, excluding outliers [b, c]	32	0.57 (0.20-1.55)	0.40 (-0.87, 1.67)	23	0.31 (0.08-1.16)	0.83 (-0.65, 2.32)

[a] The pre-specified survival analysis model included adjustment for baseline ALSFRS-R and riluzole use.

[b] Months since onset (i.e. from onset to randomization), and therefore ΔFRS, were not available for N=2 placebo patients (both A4V).

[c] The available months since onset information for N=1 A4V and N=1 non-A4V placebo patient were extreme outliers (>30 months) and questionable. These 2 patients were excluded in these analyses.

[d] Hazard ratio < 1 indicates a positive treatment effect of Arimoclomol

[e] ALSFRS-R slope difference > 0 indicates a positive treatment effect of Arimoclomol