ALS

Treatment and trials

Björn Oskarsson, MD, FAAN
Mayo Clinic Florida
Financial Disclosure

• Dr. Oskarsson receives research support from; Biogen, Mitsubishi, Genentech, Cytokinetics, Orion, Eisai, Target ALS, NINDS, and Mayo Clinic.

• Dr. Oskarsson have in the last year served as a consultant for; MediciNova, Biogen, Mitsubishi, and BioHaven.
Warning

Videotaping or taking pictures of the slides associated with this presentation is prohibited. The information on the slides is copyrighted and cannot be used without permission and author attribution.
Outcome measures

• Survival (death or >22h/24 ventilation or tracheostomy) (average 18m from diagnosis)
• Functional Rating Scale (ALSFRSr) 12 question re symptoms 0-48 (48 normal) (average -1/month)
• Quality of Life - ALSAQ5 5 question re symptoms 0-100pt (+2p/month)
• Vital capacity (forced FVC or slow SVC) % predicted (-3/month)
• Average slope rate
Combined assessment of function (ALSFRSr) and survival (CAFS)

- primary outcome takes into account both effects on survival and function

Kings Staging

- To communicate severity
- Stages 1–3 = number of El Escorial regions involved
- Stage 4 is nutritional failure-10% - gastrostomy, or respiratory failure - noninvasive ventilation (NIV)
- Stage 5 Death
- Other schemes; Japanese, Mitos

Estimating clinical stage of amyotrophic lateral sclerosis from the ALS Functional Rating Scale.
- Glutamate release inhibitor
- Sodium channel blocker
- 1.18 odds ratio of surviving 1y
  (49% placebo v. 58% riluzole)
- Increase median survival 11.8-14.8 m (n=155)
  - GBM XRT +/- Temozolomide 12.1-14.6 m
Riluzole- the trials

- 1st Bensimon
- Age 20-75
- Duration <5y
- FVC >60
- Duration 12m
- N=155
- 1’ Outcome – survival
- 2’ Function – Norris modified
- 3 other trials


<table>
<thead>
<tr>
<th>Parameters</th>
<th>Meininger et al(^{48})</th>
<th>Brooks et al(^{49})</th>
<th>Turner et al(^{50})</th>
<th>Traynor et al(^{51})</th>
<th>Mitchell et al(^{51})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment/comparator</td>
<td>Riluzole/nonriluzole treated</td>
<td>Riluzole/nonriluzole treated</td>
<td>Riluzole/nonriluzole treated</td>
<td>Riluzole/nonriluzole treated</td>
<td>Riluzole/nonriluzole treated</td>
</tr>
<tr>
<td>Design</td>
<td>Retrospective investigation on riluzole-treated vs. nontreated patients</td>
<td>Retrospective investigation on riluzole-treated vs. nontreated patients</td>
<td>Prospective investigation of therapeutic interventions including riluzole</td>
<td>Retrospective investigation on riluzole-treated vs. nontreated patients</td>
<td>Retrospective investigation on riluzole-treated vs. nontreated patients</td>
</tr>
<tr>
<td>No. patients: (total) nontreated/riluzole</td>
<td>517/161/356</td>
<td>&lt;1996: 292/241/51; ≥1996 (177) 65/112</td>
<td>(656) 349/299</td>
<td>(246) 97/149</td>
<td>(475) 327/148</td>
</tr>
<tr>
<td>Median survival time (with 95% CI if given) in overall ALS patient population: nontreated/riluzole [tracheostomy-free survival unless otherwise stated]</td>
<td>12.4 months/18.4 months p&lt;0.001 (log-rank); survival from time of diagnosis</td>
<td>&lt;1996: 47.7 (38.3–67)/58.4 (47.3–67) months p=0.1338 (log-rank); ≥1996: 49.1 (38.1–67)/≥67 (&gt;67–≥67) months p=0.0438; survival from time of symptom onset</td>
<td>32 (29–35)/51 (43–59) months p&lt;0.0001 (log-rank); survival from time of symptom onset</td>
<td>10.1/14.3 months; survival from time of diagnosis (p=0.32 log-rank; p=0.015 Peto-test)</td>
<td>2.25 (2.03–2.48)/3.07 (2.73–3.41) years; survival from time of onset; difference in median survival times (with 95% CI) for non-treated: HR 1.66 (1.32–2.12) p&lt;0.05 (log-rank)</td>
</tr>
</tbody>
</table>
UK survival predictor riluzole effect

- Without significant respiratory involvement

Knibb et al 2016
Side effects and products

- 1/200 liver toxicity, generally reversible, monitor
- ~10% GI distress, ~10% fatigue
- Mild reduction (20% in AUC with fat rich meal)
- riluzole - Rilutek®, Tiglutik™ suspension 2018
  - Riluzole cost $58 to average list price $1,120.52,
  - Biohaven product delayed
Edaravone

- FDA Approved May 2017
  - EMA application withdrawn
- Free radical scavenger
- Infusion 10-14 days on / 14 off
- N=134 x 6 months
- >1 on all 12 ALSFRS-R,
- FVC > 80%
- Definite or probable ALS EEC
- <2 y first symptom
- -1 to -4 pt. FRS/3 months
- Much more restrictive than most trials – reduced variability
- estimated $145,500 per year
- Well tolerated (3007 pt in 2018 – 1 anaphylaxis)

1) Takei ALS/FTD 2017, 2) Lancet Abe et al 2017
Is edaravone harmful? (A placebo is not a control)

JOHN TURNBULL

Department of Medicine, McMaster University, Hamilton, Canada

- Critique of study 19
- IV’s cause thrombosis, but...
  - 0 events in study 19
  - 0 in the 6 month extension
- The studied patients were early in disease
- The prior studies (16, 18) may have suggested harm later in disease – this not clear
No benefit / no harm except lower quality of life
• 30 treated vs 50 historical control
• 2 DVT’s
Biomarker Refine ALS

• Just started enrolling
• 40 US sites, 300 volunteers
• Commercial product
• Multiple biomarkers (oxidative stress, inflammation, neurodegeneration epigenetic and protein biomarkers)
Oral form

• MTB has presented a oral solution
• To go into trials late 19/ early 20
• Higher / more frequent dosing per FDA request
• Different doses as control
• 2006 Bilevel pressure support
• N=41
• improved survival (+205d) and quality of life
Ventilatory- Noninvasive positive pressure

• Basic NIV
  o Inspiratory pressure 8-10 cm H2O
  o Expiratory pressure 0-5 cm H2O
  o Back up rate

• Volume assured (AVAP, iVAPS)

• Avoid O2

• Medicare
  o FVC <50%
  o MIP <60 cm H2O
  o PaCO2 >45 mmHg
  o Nocturnal oximetry <88% for 5 minutes

Bourke et al 2006
At diagnosis if the patient already has respiratory involvement;
if NIV and bulbar involvement - mortality 20% per month
if NIV and no bulbar involvement 10% per month
if no NIV and bulbar involvement - mortality is 54%/m
if no NIV and no bulbar involvement - mortality is 31%/m
• Single center Australian registry
• Median tracheostomy free survival from symptom onset was 28 months in NIV-treated patients compared to 15 months in untreated (n=929)
Supplements

• No good quality data
L-carnitine, donor of acetyl groups increases intracellular carnitine

1g TID

N=82 x 48 week

Definite/probable ALS patients, 40-70 years of age, duration 6-24 months, self-sufficient (i.e. able to swallow, cut food/handle utensils, and walk), and FVC > 80%

34 (80.9%) ALC and 39 (97.5%) placebo became non-self-sufficient (p = 0.0296).

Mean ALSFRS-R scores at 48 weeks were 33.6 (SD 10.4) and 27.6 (9.9) (p = 0.0388)

Median survival was 45 months (ALC) and 22 months (placebo) (p = 0.0176)

- 40.5% ALC and 65.0% receiving placebo had died
FDA

- ALSA effort
- 100 experts and patients
Arlie house - WFN

Preclinical studies
Investigators should provide a firm biological rationale for moving a therapeutic candidate into human trials.
Investigators should develop preclinical pharmacodynamic and target engagement biomarkers for therapeutic candidates to inform the design of human trials whenever possible.
Investigators and research funders should commit effort, time, and funds to independent preclinical validation studies of therapeutic candidates, and publish positive and negative results, ideally in a peer-reviewed, open-access format.

Biological and phenotypic heterogeneity
Investigators should collect DNA from all participants, when possible, to allow genetic post-hoc analyses, which may reveal important stratification or screening factors for a subsequent clinical trial(s).

Outcome measures
All study examiners should undergo training to ensure uniformity of study procedures across sites and across time.

Disease-modifying and symptomatic interventions
When a symptomatic intervention is effective (e.g., NIV), the investigator should consider permitting its use for trial participants. Ethical implications and challenges to enrollment should be carefully considered if such a symptomatic intervention is used as an exclusion factor for participation.
Investigators should conduct rigorous randomized controlled trials of symptomatic therapies or medical devices and utilize a patient-reported outcome and QOL measure as either a primary or secondary outcome in such trials.

Recruitment and retention
Investigators should ensure ALS clinical trial results are published in open-access journals.

Biomarkers
In designing and implementing ALS clinical trials, investigators should incorporate (to the extent that they have been developed and validated as such) predictive biomarkers, prognostic biomarkers, and, especially in phase 2 trials, pharmacodynamic biomarkers.
Investigators should ensure that biomarkers are quantifiable and can be measured reliably using standardized operating procedures across multiple centers, accounting for relevant sources of variability, including intrasubject and intersubject, intraassessment and interassessment (assay, evaluator, scanner), and interlaboratory/site.

Clinical trial phases
Investigators should carefully review phase 2 trial results and choose a primary endpoint that is clinically meaningful and adequately powered for phase 3.
When designing phase 3 trials, investigators should seek to use placebo-control before considering alternative designs.
Investigators should publish all clinical trial results, negative or positive, so they are widely available to the ALS community.

ALS, amyotrophic lateral sclerosis; NIV, non-invasive ventilation; QOL, quality of life. Adapted from [1].

Active trials

Phase 3
1. A Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BIIB067 Administered to Adult Subjects With ALS and Confirmed Superoxide Dismutase 1 Mutation (VALOR)
2. A Phase 3, Randomized Double-Blind, Placebo-Controlled Multicenter Study to Evaluate Efficacy and Safety of Repeated Administration of NurOwn® (Autologous Mesenchymal Stem Cells Secreting Neurotrophic Factors) in Participants With ALS
4. Open Label, Non-randomized Extension Trial to Assess Long Term Safety and Efficacy of Arimoclomol in Subjects With ALS Who Have Completed the ORARIALS-01 Trial
5. Safety and Efficacy of TUDCA as add-on Treatment in Patients Affected by ALS (TUDCA-ALS)

Phase 2
1. Conservative Iron Chelation as a Disease-modifying Strategy in Amyotrophic Lateral Sclerosis (FAIR-ALS II) Frances
2. Safety and Tolerability of Perampanel in Amyotrophic Lateral Sclerosis Patients Lebanon
3. Open-label Clinical Trial of Lacosamide in ALS Japan
4. MIROCALS: Modifying Immune Response and Outcomes in ALS (MIROCALS) UK France
5. Rapamycin Treatment for ALS (RAP-ALS) Italy
6. Safety of Urate Elevation in Amyotrophic Lateral Sclerosis (ALS) (SURE-ALS2) MA, FL
7. Clinical Trial of Ultra-high Dose Methylcobalamin for ALS Japan
8. Inhibition of Rho Kinase (ROCK) With Fasudil as Disease-modifying Treatment for ALS (ROCK-ALS) Germany
9. A Clinical Trial of Pimozide in Patients With Amyotrophic Lateral Sclerosis (ALS) (Pimozide2) Canada
10. Study on the Safety, Tolerability and Efficacy of Cannabis Based Medicine Extract (t CBD Oil) in Slowing the Disease Progression in ALS Birmingham, West Midlands UK
11. A Phase II Pilot Single-arm Safety and Tolerability Study of ILB a type of low molecular weight dextran sulfate, in Patients With MND (ALS), Kansas City, Kansas
12. A Phase II Study of Intrathecal Autologous Adipose-derived Mesenchymal Stromal Cells for Amyotrophic Lateral Sclerosis Rochester, Minnesota
13. A Study to Evaluate Transplantation of Astrocytes Derived From Human Embryonic Stem Cells, in Patients With Amyotrophic Lateral Sclerosis (ALS) Jerusalem
15. Multi-centered Double Blind, Placebo Controlled Study Evaluating the Safety and Efficacy of Memantine in Patients With ALS Currently Taking Riluzole Kansas City, Kansas
16. Safety and Efficacy of Ranolazine for the Treatment of Amyotrophic Lateral Sclerosis Kansas City, Kansas
17. The Effect of RNS60 on ALS Biomarkers Milano
18. Tolerability and Efficacy of L-Serine in Patients With Amyotrophic Lateral Sclerosis: A Phase Ila Study New Hampshire
19. A Clinical Trial to Evaluate the Safety and Efficacy of Perampanel in Subjects With Amyotrophic Lateral Sclerosis (ALS) New York, New York
Active Early phase
- list incomplete

1. Perampanel Single Ascending Dose Transcranial Magnetic Stimulation Biomarker Study in Amyotrophic Lateral Sclerosis
   Jacksonville, Florida
2. T-regulatory Cells in ALS
   Houston, TX
3. A Multicenter, 18-week Open Label Safety and Efficacy Trial of Dalfampridine in Primary Lateral Sclerosis
   Gainesville, TX
4. Phase 1b Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of DNL747 in Subjects With ALS
   Orlando, FL
5. A Phase 1, Single-Ascending-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BIIB100 in ALS
   USF other
6. A Pilot Study of Lung Volume Recruitment Combined With Expiratory Muscle Strength Training in ALS
   Gainesville, FL
7. A Pilot Study to Assess Transmembrane Electromyography for the Assessment of Neuromuscular Function in the Oropharynx
   San Diego, CA
8. Acute Intermittent Hypoxia and Breathing in Neuromuscular Disease
   Gainesville, Florida
9. An Open-Label Pilot Study Comparing the Efficacy of SSRIs Versus TCAs for Treating Depression in ALS
   Saint Louis, Missouri
10. BrainGate2: Feasibility Study of an Intracortical Neural Interface System for Persons With Tetraplegia
    Boston, Massachusetts
11. HERV-K Suppression Using Antiretroviral Therapy in Volunteers With Amyotrophic Lateral Sclerosis (ALS)
    Bethesda, Maryland
12. Impact of Nuedexta on Bulbar Physiology and Function in ALS
    Gainesville, Florida
13. Investigation on the Cortical Communication (CortiCom) System
    Baltimore, MA
14. Non-invasive Brain Stimulation for the Treatment of Depression Symptoms in ALS: A Pilot Study
    New York, New York
15. Noninvasive Cervical Electrical Stimulation for ALS: Mechanistic and Safety Study
    Bronx, New York
16. Treatment of FUS-Related ALS With Betamethasone - The TRANSLATE Study
    Lexington, Kentucky
Survival $1.4\pm0.7$ years for SOD1$^{A4V}$
SOD1 ASO

Antisense Drug Therapy:

RNase H-mediated RNA degradation (tofersen, BIIB078, BIIB080)

Adapted from Niemietz et al., 2015
Interim safety, PK, and PD results of tofersen phase 1/2 study

Tofersen was generally well tolerated at doses up to and including 100 mg

Most AEs were mild or moderate in severity, and included headache, procedural pain, and post-lumbar puncture syndrome

CSF exposure of tofersen and SOD1 target engagement were greatest in the 100 mg treatment arm

- Maximal reduction of CSF SOD1 level at Day 85 observed in participants treated with tofersen 100 mg (average 37% reduction) vs. no reduction in placebo group, p=0.002

Treatment with tofersen was associated with a trend toward lowering pNFH levels in the CSF

Values below limit of quantitation are set to zero at day 1 predose and set to half of lower limit of quantitation (1 ng/mL) at other time points in calculation.

AE = adverse event
Interim exploratory efficacy results: tofersen 100 mg demonstrated a slowing of decline across clinical measures

Consider testing for referral to trial? Only fast-progressing slots available
A Study to Assess the Safety, Tolerability, and Pharmacokinetics of BIIB078 in Adults With C9ORF72-Associated ALS

- Actual Study Start Date: September 10, 2018
Treatments of genetic forms

- Biogen/Ionis
- Wave Life
- Avexis/Novartis
- CRISPR therapeutics
Mesenchymal Stromal Cell Therapies for Neurodegenerative Diseases


Nathan P. Staff, MD, PhD; David T. Jones, MD; and Wolfgang Singer, MD
Repeated Intrathecal Mesenchymal Stem Cells for Amyotrophic Lateral Sclerosis

Ki-Wook Oh, MD, PhD, Min-Young Noh, PhD, Min-Soo Kwon, MD, PhD
Hyun Young Kim, MD, PhD, Seong-il Oh, MD, PhD, Jinsok Park, MD
Hee-Jin Kim, MD, PhD, Chang-Seok Ki, MD, PhD, and Seung Hyun Kim, MD, PhD
Safety of intrathecal autologous adipose-derived mesenchymal stromal cells in patients with ALS

- $1 \times 10^7$ (single dose) to $1 \times 10^8$ cells (2 monthly doses)
Original Investigation

Safety and Clinical Effects of Mesenchymal Stem Cells Secreting Neurotrophic Factor Transplantation in Patients With Amyotrophic Lateral Sclerosis Results of Phase 1/2 and 2a Clinical Trials

Panayiota Petrou, MD; Yael Gotelf, PhD; Zohar Argov, MD; Marc Gotkine, MD; Yossef S. Levy, PhD; Ibrahim Kassis, PhD; Aci Valkin-Dembinsky, MD; Tamir Ben-Hur, MD; Daniel Offen, PhD; Oded Abramsky, MD; Eidad Melamed, MD; Dimitrios Karussis, MD, PhD

- 14 patients open label
- -5.1 to -1.2%/m ΔFVC, P <.04
- -1.2 to -0.6 ΔALSFRS/m, P =.05
- Phase III ongoing
- N=200 participants
- Close to completing enrolment (start 2017)

JAMA Neurol. 2016 Mar;73(3):337-44
Perampanel

• Targeting neuronal hyperexcitability Anti-AMPA
• AMPA mediated
• Mayo Clinic – Eisai – University of California Davis
• Phase II’s in Buffalo and Lebanon
• Phase III to start in Japan
Reldesemtiv

- Slows the rate of Ca release from the troponin complex of fast skeletal muscle, sensitizes the sarcomere to Ca, leading to increase in skeletal muscle contractility
- Presented not published
- N=458 (1:1:1:1) x 12 week
- 150 mg, 300 mg or 450
- -27% slowing of in SVC
- -25% slowing of ALSFRS-R

Cytokinetics website
Oral levosimendan (ODM-109): Key placebo-controlled results from the phase 2 study in ALS patients with SVC between 60-90% predicted at screening

Ammar Al-Chalabi, Pamela Shaw, P. Nigel Leigh, Leonard van den Berg, Orla Hardiman, Albert Ludolph, Toni Sarapohja, Mikko Kuoppamäki

1 King’s MND Care and Research Centre, King’s College London, UK, 2Sheffield Institute for Translational Neuroscience, University of Sheffield, UK, 3Brighton and Sussex Medical School, University of Sussex, UK, 4University Medical Center Utrecht, Netherlands, 5Trinity Biomedical Sciences Institute, Trinity College Dublin, Ireland, 6Department of Neurology, University of Ulm, Germany, 7Orion Pharma, Finland

BACKGROUND
Levosimendan (i.v.) is approved for the acute worsening of severe chronic heart failure (CHF) in over 60 countries. Levosimendan sensitizes also skeletal muscle fibres to calcium by binding selectively to troponin C. Based on these findings, oral levosimendan (ODM-109) is now under development in ALS.

OBJECTIVES
To study oral levosimendan in a phase 2 study (LEVALS) in ALS.

METHODS
- LEVALS was a randomized, double-blind, placebo-controlled, 3-period, cross-over phase 2 study with a 6 month open-label extension
- Study treatments were placebo and 1 mg and 2 mg daily doses of levosimendan
- Each treatment period lasted for 14 days separated by wash-out periods
- Primary endpoint was sitting SVC and secondary endpoints included e.g. supine SVC and ALSFRS-R

- Sensitizes skeletal muscle fibers to calcium by binding selectively to troponin C
- Current international phase III,
- Fully enrolled 450 patients x 48 week
2020 Trials
Ibudilast (MN-166)

- orally bioavailable, small molecule
- small molecule phosphodiesterase (PDE) -4 and -10 inhibitor and a macrophage migration inhibitory factor (MIF) inhibitor
- approved in Japan 1989 - post-stroke complications and bronchial asthma
- Ibudilast has been prescribed to over 3.2 million patients and has a good post-marketing safety profile.
- Completed phase 2
- Phase 3 starting 2020

<table>
<thead>
<tr>
<th>ALSFRS-R Total Score</th>
<th>MN-166 + riluzole</th>
<th>Placebo + riluzole</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early ALS subgroup</td>
<td>Responders (&lt;2 ΔFRS)</td>
<td>30.0% (6/20)</td>
<td>9.1% (1/11)</td>
</tr>
<tr>
<td></td>
<td>Improvers (+ ΔFRS)</td>
<td>25.0% (5/20)</td>
<td>0.0% (0/11)</td>
</tr>
<tr>
<td>Early ALS + NIV</td>
<td>Responders (&lt;2 ΔFRS)</td>
<td>26.9% (7/26)</td>
<td>7.7% (1/13)</td>
</tr>
<tr>
<td></td>
<td>Improvers (+ ΔFRS)</td>
<td>23.1% (6/26)</td>
<td>0.0% (0/13)</td>
</tr>
</tbody>
</table>
Platform

ONE TRIAL

3-5 treatments now …
perpetual infrastructure!

• Zilucoplan, a small macrocyclic peptide inhibitor of complement component 5 [C5], Ra Pharmaceuticals, Inc.

• Verdiperstat, an oral myeloperoxidase inhibitor, - by Biohaven

• Bioenergetic Nanocatalysis (CNM-Au8, nanocrystalline gold) - by Clene Nanomedicine, Inc.
Trials and research

• Encourage patients to participate in biomarker studies (blood, CSF and tissue)
• Without a good understanding of the pathophysiology, a cure is unlikely
• Look for projects at Ct.gov and NEALS trials finder
• Match to projects by joining the National Registry
• Encourage brain donation (and organ donation)
END
Treatment and trials

Which of the following interventions is estimated to have the strongest affect on prolonging life in ALS?

A. edaravone
B. gastrostomy
C. noninvasive ventilation
D. riluzole
Treatment and trials

Which of the following common ALS symptoms does not have any proven treatment?

A. Muscle cramps
B. Pseudobulbar affect
C. Fatigue
D. Fasciculations
Treatment and trials

How much is the rate of ALS progression ($\Delta$FRSr) slowed by edaravone vs. placebo?

A. 0%
B. 10%
C. 25%
D. 33%
Treatment and trials

ALS is the only neurological disease tracked by the CDC-Agency for Toxic Substances and Disease Registry. As a neurologist you should;

A. Report ALS like you would other reportable diseases.
B. Encourage all ALS patients to join the registry.
Treatment and trials

No specific therapies are approved for genetically determined forms of ALS. Which genetic form of the disease has trial data suggesting almost halting of progression?

A. SOD1
B. C9orf72
C. TARDBP
D. FUS
Share Your Feedback

• Please use the 2019 AANEM Annual Meeting app to rate this presentation and the speaker(s).

• Your feedback helps us enhance our annual meeting to ensure we are continuing to meet your needs.
• Claiming CME
• Course and Plenary Presentations

Visit: www.aanem.org/resources

Record your attendance hours after each session or do it all at once after the meeting is complete! Credit not recorded by December 15, 2019 will not be reported to ABPN and ABPMR. The AANEM will report ALL Annual Meeting attendees’ credit to ABPN and ABPMR by December, 31, 2019.
Extra slides
• urate as an endogenous antioxidant and neuroprotectant
• high urate levels correlate with improved survival in epidemiological studies
• Safety of Urate Elevation in Amyotrophic Lateral Sclerosis (SURE-ALS2)
El Escorial for research

<table>
<thead>
<tr>
<th>Definite ALS</th>
<th>Presence of upper motor neuron and lower motor neuron signs in the bulbar region and at two of the other spinal regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable ALS</td>
<td>Presence of upper motor neuron and lower motor neuron signs in at least two regions with upper motor neuron signs rostral to lower motor neuron signs</td>
</tr>
<tr>
<td>Probable ALS, laboratory results supported</td>
<td>Presence of upper motor neuron and lower motor neuron signs in one region with evidence by EMG of lower motor neuron involvement in another region</td>
</tr>
<tr>
<td>Possible ALS</td>
<td>Presence of upper motor neuron and lower motor neuron signs in one region or upper motor neuron signs in two or three regions, such as monomelic ALS, progressive bulbar palsy, and primary lateral sclerosis</td>
</tr>
</tbody>
</table>

*ALS, amyotrophic lateral sclerosis; EMG, electromyography.*
Protein chaperone

N=38

Survival favored arimoclomol with a hazard ratio of 0.77 (95% CI 0.32-1.80).

ALSFRS-R and FEV6 declined more slowly in the arimoclomol group, differences of 0.5 point/month (95% CI -0.63 to 1.63) and 1.24 percent predicted/month (95% CI -2.77 to 5.25),

CAFS similarly favored arimoclomol.
A Phase 3, Randomised, Placebo-Controlled Trial of Arimoclomol in Amyotrophic Lateral Sclerosis

- sALS and fALS
- Enrollment completed n=231
- Open label extension open
AMX0035 IN PATIENTS WITH ALS (CENTAUR)

- Enrollment complete (n=132)
- tauroursodeoxycholic acid (TUDCA) + sodium phenylbutyrate (PB)