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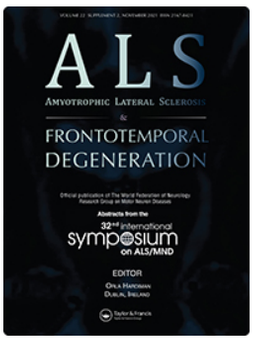

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Theme 09 - CLINICAL TRIALS AND TRIAL DESIGN

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THEME 9 CLINICAL TRIALS AND TRIAL DESIGN

CLT-01 RNS60 in ALS: Expanded Access Program

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Background: RNS60 is an electrokinetically altered aqueous fluid composed of saline and oxygen that has demonstrated neuroprotective and anti-inflammatory effects in both *in vitro* and *in vivo* models of ALS and other neurodegenerative diseases. RNS60 has been tested in 7 clinical pharmacology studies, in which it was well tolerated, and is in Phase II clinical testing for the treatment of amyotrophic lateral sclerosis (ALS). It can be administered by IV infusion and inhalation (nebulization). We designed an intermediate-size Expanded Access Program (EAP) to treat up to sixty ALS patients with RNS60 for up to 3 years. EAPs provide a means for patients who do not qualify for controlled clinical trials to access experimental drugs. These are often patients in the advanced stages of their disease. The objectives of this ongoing EAP are to provide investigational treatment of RNS60 for people with ALS who do not qualify for a clinical trial, establish the feasibility of EAPs in people with ALS, and monitor the safety and tolerability of long-term RNS60 administration.
Methods: Participants are treated with twice-daily inhalation of nebulized RNS60 at home for up to 3 years. In addition, two participants receive once-weekly IV RNS60 in addition to nebulized RNS60 and one participant exclusively receives weekly IV RNS60 infusions. Participant safety is monitored through the collection of safety labs and the assessment of adverse events (AEs). We also administered the ALS functional rating scale revised (ALSFRS-R), measured slow vital capacity (SVC), and collected patient-reported experience questionnaires. Blood samples are collected for the measurement of soluble biomarkers in plasma and for functional assessment of regulatory T cells (Tregs).
Results: 49 participants with ALS have been enrolled and treated with RNS60. 28 participants have completed six months of RNS60 treatment, 12 participants have completed 12 months of treatment, 5 participants have completed 18 months of treatment, and 3 participants have completed 24 months of treatment. Average age at baseline was 60.8 and average ALSFRS-R at baseline was 19.7. 10 participants have died due to complications related to ALS disease progression. No serious adverse events (SAEs) related to RNS60 have occurred and no participants have withdrawn from the program due to drug-related adverse events. This EAP has been well-accepted by the participating ALS patients and their caregivers.
Conclusions: This EAP demonstrates the feasibility of performing EAPs in ALS patients as a complimentary approach to controlled clinical trials that allow for the collection of longer-term safety data. Overall, tolerability for and compliance with RNS60 treatment was high, which demonstrates the feasibility of RNS60 treatment in a broad ALS population, particularly those in the advanced stages of ALS disease progression.

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CLT-02 The REFALS-ES open-label extension study of oral levosimendan in people with ALS

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Background: There is an unmet need for new therapies in amyotrophic lateral sclerosis (ALS). Levosimendan is a calcium sensitizer that enhances myocyte contractility by selectively binding to troponin C in myocardium and slow-twitch skeletal muscle. Levosimendan was shown to improve diaphragm neuromechanical efficiency in healthy volunteers and to have positive effects on supine slow vital capacity (SVC) (post-hoc) in the LEVALS study in people with ALS. These effects were to be confirmed in the REFALS study: a randomized, double-blind, placebo-controlled phase 3 trial involving 496 participants with ALS and sitting SVC between 60% and 90% of predicted. Neither the primary (change from baseline in supine SVC at 12 weeks) nor the key secondary

endpoint (combined assessment of function and survival (CAFS), including the revised ALS functional rating scale (ALSFRS-R) of the trial were met. Participants completing the REFALS study were provided an option to continue treatment with levosimendan in an open-label extension, the REFALS-ES study, evaluating the long-term safety and efficacy of oral levosimendan in ALS. Results of the REFALS-ES study are presented here.

Methods: REFALS-ES included participants completing 48 weeks of treatment according to the REFALS study protocol, who were able to swallow the study treatment capsules and had not developed any new (or significant worsening of existing) illness, such as serious cardiovascular disease. The participants were treated with oral levosimendan 0.5–2 mg daily and followed up with clinic or remote visits at least every 3 months and reassessment 2 weeks after each dose change. The efficacy assessments included sitting and supine SVC, ALSFRS-R, need for respiratory support, and Borg Category Ratio 10 (CR 10) scale on dyspnea. Safety was assessed by adverse events (AEs), vital signs, 12-lead electrocardiogram and suicidality.

Results: A total of 227 REFALS participants entered the study and received oral levosimendan for a mean of 24 (range 0.3–61.0) weeks. At 6 months from baseline, the supine and sitting SVCs had declined by −3.3 and −3.2 %points, respectively, ALSFRS-R total score by −3.4 points, with similar changes in all the four subdomains (−0.8–0.9 points), and Borg CR 10 had increased by 1.1 and 0.8 points for supine and sitting, respectively. Non-invasive ventilation was started by 15% of the participants during the study. Treatment-emergent AEs (TEAEs) were recorded in 71%, serious TEAEs in 19%, discontinuations due to TEAEs in 7% and deaths in 8% of the participants. The most frequently reported TEAEs were fall, headache and tachycardia. Increase in pulse and heart rate was seen during treatment with levosimendan.

Discussion: The study showed a decline in all the efficacy outcome measures, the magnitude of which was less than expected for the SVC, possible reflecting selection bias in participants completing the REFALS study. No new safety concerns were identified.

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CLT-03 Pharmacokinetics and bioequivalence of an investigational oral formulation of edaravone (MT-1186) in patients with amyotrophic lateral sclerosis

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Background: Radicava® (edaravone injection) is a US Food and Drug Administration-approved treatment for ALS that slows the rate of physical functional decline (1,2). As intravenous (IV) administration can burden patients, orally administered treatments are needed.

Objectives: To assess the pharmacokinetics (PK) and bioequivalence of an oral suspension formulation of edaravone (MT-1186) compared with the already approved intravenous edaravone.

Methods: Three open-label phase 1 clinical studies were conducted in healthy subjects or in patients with ALS with or without percutaneous endoscopic gastrostomy (PEG). Study J03 was a single-dose, crossover, bioequivalence study involving 42 healthy subjects who received 105 mg of oral edaravone and IV edaravone (60 mg/60 min) (3). Assessments included PK parameters, metabolic profiles, and elimination pathways for each formulation. The 24-h PK of a single dose of investigational oral edaravone was also assessed in 9 patients with ALS (Study J04) and in 6 patients with ALS who had PEG tubes (Study J05).

Results: In healthy volunteers (Study J03), the geometric mean ratios and 90% confidence intervals (CIs) of area under the plasma concentration-time curve (AUC) and the geometric mean ratio and its lower limit 90% CI of maximum serum concentration (Cmax) of the 105-mg oral suspension compared with the 60-mg IV formulation met bioequivalence limits. Both formulations showed quite similar triphasic plasma concentration-time profiles of edaravone after reaching Cmax. Edaravone in both routes underwent urinary excretion, mainly as the glucuronide conjugate and, to a lesser extent, as the sulfate conjugate. Urinary relative composition ratios of unchanged edaravone and metabolites were similar for both formulations. One subject in each group experienced an adverse event (AE), both of which were mild in severity and were not judged to be related to edaravone by the investigator.

In patients with ALS (Study J04), the investigational, oral edaravone was well absorbed after the oral administration and showed triphasic plasma concentration-time profiles of edaravone after reaching Cmax, as in the healthy subjects. The single dose of investigational, oral edaravone was well tolerated, with 1 treatment-emergent AE (TEAE) reported in 1 patient. The TEAE was mild in severity and was judged not to be reasonably related to the investigational product by the investigator. Similar results were obtained in the study with ALS patients who had PEG tubes (Study J05).

Discussion: These studies provide clinical evidence for the bioequivalence and tolerability of the investigational, oral edaravone and will help support the development of MT-1186 for patients with ALS.

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References

1. RADICAVA® (edaravone injection) [package insert]. Jersey City, NJ: Mitsubishi Tanabe Pharma America, Inc; 2021.
2. Writing Group; Edaravone (MCI-186) ALS 19 Study Group. Lancet Neurol. 2017;16(7):505–12.
3. Shimizu H, et al. Clin Pharmacol Drug Dev. 2021. [Epub ahead of print].

CLT-04 An open-label trial of Clenbuterol in people with ALS

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Background: Clenbuterol, a beta-agonist, has plausible mechanisms for treating ALS (1). Clenbuterol treatment preserved motor function and prolonged survival in a mouse model of ALS (2), and a low dose improved limb strength and FVC over 6 months in a series of 16 Italian patients (3).
Methods: Based on this promising background, we conducted a widely inclusive open label trial of Clenbuterol in 25 people with ALS. All received clenbuterol starting at 40 mcg QD, ramping up to 80 mcg BID. Outcomes included safety, tolerability, ALSFRS-R progression, FVC progression, hand grip dynamometry, and upper and lower limb myometry. ALSFRS-R and FVC slopes measured during treatment were compared to slopes prior to treatment (calculated by assuming ALSFRS-R was 48 and FVC was 100% at ALS onset). Missing ALSFRS-R and FVC values were imputed from the available data points.
Results: The 25 participants had a mean age of 59, mean disease duration of 43 months, ALSFRS-R score at enrollment 34, FVC at enrollment 77%. 48% were female, 68% were taking Riluzole, none were taking Edaravone. Two participants experienced SAEs, neither related to the study. Twenty-four participants experienced AEs, most commonly tremors/jitters, cramps/spasms, insomnia, and stiffness/spasticity. Fourteen participants withdrew early from the trial, 13 due to AEs. Patients who withdrew early were significantly older and more likely to be male. Per-protocol and intention-to-treat analyses showed meaningfully slower ALSFRS-R and FVC progression during treatment. Hand grip dynamometry and myometry changes were highly variable between participants; most declined slowly but some showed improvements.
Conclusions: Clenbuterol was safe but less tolerable at the doses we selected compared to an earlier Italian case series (3). Consistent with that series, our study suggested benefits on ALS progression. Our study is limited by small sample size, large drop out, lack of randomization, blinding and placebo-controls. A larger more traditional trial now appears warranted.

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References

1. Bartus R, Betourne A, Basile A, et al. Neurobiol Dis. 2016;85:11–24.
2. Teng Y, Choi H, Huang W, et al. Neurosci Lett. 2006;397:10–7.
3. Soraru G, Pegoraro E, Spinella A, et al. Amyotroph Lateral Scler. 2006;7:246–248.

CLT-05 COVID-19 mitigation strategies utilized in the Radicava/edaravone findings in biomarkers from ALS (REFINE-ALS) study

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Background: The sudden onset of the COVID-19 pandemic profoundly affected clinical trial patient recruitment, enrollment, and retention. Most medical clinics underwent significant reductions in patient visits to accommodate social distancing and lockdown regulations. As a result, a variety of strategies were employed to mitigate the impact of COVID-19 on clinical trial management. Most trial strategies focused on continuing to evaluate safety, rather than complex biomarkers. The REFINE-ALS study focused on continuing to collect biofluids requiring complex processing for biomarker evaluation.
Objective: The REFINE-ALS study will identify putative biomarkers to serve as quantifiable biological nonclinical measures of the pharmacodynamic effect of edaravone in ALS and evaluate its effectiveness in people with ALS in real-world settings. Key strategies used to mitigate COVID-19 challenges in REFINE-ALS are described.
Methods: REFINE-ALS is a prospective, observational, longitudinal, multicenter US study that will enroll up to 300 adults with ALS who will initiate Radicava® (edaravone injection) treatment. Selected biomarkers, including those for oxidative stress, inflammation, neuronal injury and death, and muscle injury, will be evaluated. Other clinical efficacy assessments include ALS Functional Rating Scale Revised, King's clinical staging, ALS Assessment Questionnaire long form, slow vital capacity (SVC), and time to specified states of disease progression or death. DNA samples will be collected for genomic sequencing. Adverse events related to the study will be reported.
Results: Study enrollment began in October 2019, and within months, was affected by COVID-19. In the early months of 2020, most participating sites reported strict institutional restrictions on in-person visits for observational studies, requiring cessation of patient enrollment. Site activations slowed, some already-activated sites closed, patient recruitment slowed or halted, and most enrolled participants were unable to visit clinical sites. Moreover, global supply chain limitations caused delays in the availability of laboratory kits for sample collection, and closure of research laboratories prevented processing of specimens.
Mitigation strategies were deployed through protocol amendments. Multiple home health agencies and home spirometry vendors were assessed to find the best solutions. Workflows were developed to perform and document at-home visits by trained healthcare clinicians to collect blood samples, perform clinical assessments, and measure SVC. Informational webinars for study investigators were held in autumn 2020 to inform sites of upcoming protocol changes, and remote-visit training for sites was conducted in early 2021.
As of April 2021, 33 sites have been activated, including 32 US sites and 1 Canadian site. A total of 33 patients were enrolled as of June 2021.
Discussion: The COVID-19 mitigation strategies employed in the REFINE-ALS study may be applicable to other clinical studies in ALS and may help improve clinical trial procedures in future studies.

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CLT-06 An assessment of the ALSFRS-R by the ALS community: a mixed-methods study

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Background: The Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) is the most commonly used outcome measure in ALS clinical trials.
Objectives: The objective of this study is to identify potential limitations in the ALSFRS-R from a patient and caregiver perspective.
Methods: This study was reviewed and waived by North Star Institutional Review Board. An online survey was conducted via SurveyMonkey from 15 June 2021 to 2 July 2021. Study enrollment was open to all patients diagnosed with ALS or caregivers of people who currently have or who passed away from ALS. Participants were presented with each of the 12 items in the ALSFRS-R and asked a series of questions about each item. A qualitative content analysis was conducted to capture overarching themes. Quantitative analysis was performed with SPSS version 27. Qualitative data were analyzed with NVivo.
Results: A total of 103 people responded to the survey, of whom 67% are people with ALS and 33% are caregivers. Participants originated from 17 countries, of which 32 (31%) are from the United States. The mean age of the participants was 50, and 47% identified as male. The mean most recent ALSFRS-R score, if known, was 31.4 (SD 11.8; range 1–48). Forty-seven (46%) individuals expressed concerns about their ability to accurately answer at least one item of the scale. Most individuals had concerns about item 1 (speech), item 8 (walking), and item 5 (cutting food). The majority of comments fell into one of the following categories: language used in the question is of a literacy level too high for most people with ALS; language used is of appropriate literacy level but needs clarity; the question is answered differently depending on the situation or equipment used; it is difficult to distinguish the difference between choices on the scale; and the structure and/or underlying assumptions of the question makes it difficult to answer.
Discussion: In this study, we found that nearly half of the patients indicated concerns that parts of the ALSFRS-R do not accurately reflect their ability. Though improving language may address some of these concerns, there is need to critically revise items to accurately capture the patient's functioning.

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CLT-07 Longitudinal comparison of self-reported ALSFRS-R and ROADS questionnaires in people with ALS

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Background: Patient-reported outcome measures are of increasing importance for ALS research. The Revised ALS Functional Rating Scale (ALSFRS-R) is a primary outcome measure in most clinical trials for people with ALS (PALS). Recent studies have highlighted limitations of the ALSFRS-R – it is not linearly weighted, many PALS show no change over 6 months, some scores can improve with changes in symptom management, and though it is scored ordinally, the clinical meaning of a one-point change varies by question. Given these limitations, the Rasch-Built Overall ALS Disability Scale (ROADS) was developed with a focus on psychometric performance in an effort to capture functional changes in ALS as an outcome measure for ALS trials.
Objective: The data collected in this study will be used to (1) understand the characteristics of the self-reported version of the ALSFRS-R and ROADS to quantify clinical changes in ALS and (2) compare the longitudinal characteristics of these scales.
Methods: PALS consented and enrolled for this survey study online. They were asked to complete self-reported ALSFRS-R and ROADS questionnaires at baseline, 3-, 6-, 9- and 12-months. The study is ongoing. We report results of the baseline through 6-month follow-up.
Results: As of now, 260 people consented to the study, 182 PALS completed baseline surveys, 145 completed the 3-month surveys, and 120 have completed the 6-month surveys. At baseline, the ALSFRS-R (mean =31, sd =9) and ROADS normed score (mean =79, sd =16) demonstrate a high correlation ($r = 0.89$; $p < 0.001$). For the 113 PALS with complete month 3 follow-up and 82 PALS with complete month 6 follow-up, comparing a worsening of symptoms of at least 1 point in ALSFRS-R and ROADS we see agreement of 73% (kappa =0.41, $p < 0.001$) at month 3 and 76% (kappa =0.43 $p < 0.001$) at month 6. Average change per month in total ALSFRS-R at 3 and 6 months were −0.67 ($n = 135$, sd =1.23) points and −0.48 ($n = 95$, sd =0.87) points, respectively. Average change per month in ROADS normed scores at 3 and 6 months were −0.99 ($n = 115$, sd =3.17) and −1.03 ($n = 83$, 1.83), respectively.
Discussion/Conclusions: Initial findings suggest that self-reported ALSFRS-R and ROADS are significantly correlated cross-sectionally but more work is needed to describe and evaluate differences in changes over time. The ROADS may capture more linear changes over time.

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CLT-08 Can bias and discrimination impact the ALS/MND patient experience?

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Background: ALS/MND presents a unique set of biomedical, social, and clinical research challenges, given that the condition has no known etiology or cure. Global research efforts have shown that prevalence studies, disease databases, and clinical trial enrollment within the ALS/MND space are significantly imbalanced by race and ethnicity which are largely subsumed by white participants. Within multi-national and global trials, the inclusion of Black people and people of color is often limited and not reflective of the local

population where participants are enrolled. It has been documented across high-income western countries that histories of systemic inequality and structural discrimination impact healthcare access and medical treatment, which is why it is particularly important to understand how these social realities impact a rare disease like ALS/MND.
Objective: To date, only two studies (1,2) have noted unique disparities that exist between Black and white persons with ALS/MND but none have sought to explain the reasons that disparities exist for Black persons with ALS (B-pALS). This study seeks to fill this gap.
Methods: This study was an empirically driven ethnographic investigation over 24 months. Research methods included participant observation at three multi-disciplinary ALS clinics in the United States, 86 semi-structured interviews with Black and white American ALS patients, caregivers, clinical researchers and care providers, a survey tool, and content analysis of ALS resources.
Results: Findings revealed four major themes central to the care experiences of B-pALS navigating US healthcare systems: (1) Clinicians held beliefs that supported racial science and believed biological differences existed between Black and white pALS. (2) All B-pals experienced structural and/or individual racism when interacting with clinical care providers. (3) B-pALS did not receive a timely diagnosis, or a diagnosis at all, of ALS/MND. Diagnosis in B-pals took 13 months longer compared to white pALS. (4) Some B-pALS lived shorter lives, on average 6.5 months, with ALS from diagnosis to death than white pALS.
Discussion: The four central themes identified in this investigation provide a framework for acknowledging and addressing biases towards B-pALS and other people of color pALS. Many studies have revealed that experiences of bias and racism impact physical and mental health. Bias, discrimination, and racism in the ALS care space determinately impact diagnosis, treatment, life expectancy, and clinical research. More intentional work in this area will not only create more equitable care for all living with ALS but also improve clinical research trials towards a cure.

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References

1. Qadri S, Langefeld CD, Milligan C, et al. Racial differences in intervention rates in individuals with ALS: a case-control study. Neurology. 2019;92(17):e1969–74.
2. Brand D, Polak M, Glass JD, et al. Comparison of phenotypic characteristics and prognosis between black and white patients in a tertiary ALS clinic. Neurology. 2021;96(7):e840–4.

CLT-09 Successful launch of the HEALEY ALS Platform Trial during the COVID-19 pandemic: protocol amendments and operational changes to make the trial "COVID-resilient" and ensure robust enrollment and high data quality

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Background: The HEALEY ALS Platform Trial was scheduled to launch in March 2020 with three novel investigational products and a fourth scheduled to start six months later. The trial uses a common Master Protocol at over 50 sites of the NEALS Consortium in the U.S. (NCT Number: NCT04297683). In March 2020, the COVID-19 pandemic caused widespread research and societal restrictions that continued for at least 1 year.
Objective: To report rapidly-implemented adjustments to make the HEALEY ALS Platform trial "COVID-resilient" and enable the trial to initiate and sustain enrollment safely and effectively.
Methods: A COVID-19 Task Force was assembled in March 2020 and included ALS investigators with experience in telemedicine and digital tools, clinical operations staff, and regulatory experts. The Task Force engaged with multiple stakeholders including industry partners, the trial's Central IRB, site investigators, vendors, and the patient community to identify the most effective path forward in an uncertain environment. Criteria used to evaluate possible options were safety of trial participants and site staff, scientific impact, operational feasibility including cost, participant and site burden, compliance with regulations (IRB, FDA), and geographic distribution of COVID-related restrictions.
Results: Because the Platform Trial is conducted under centralized infrastructure, protocol changes recommended by the COVID-19 Task Force were implemented rapidly. Pulmonary function was collected using coached home spirometry on a portable device. Telemedicine was added for follow-up study visits and collection of the revised ALS Functional Rating Scale (ALSFRS-R). Vital signs and safety labs were outsourced to a home nursing vendor or local laboratory. The electronic data capture system was modified to capture COVID-related deviations as required by the FDA. Site monitoring has been completed using remote monitoring visits. With these modifications, the trial enrolled the first participant in July 2020 and has met the target rate of approximately 1 participant enrolled/site/month. Data completeness has been high.
Discussion: The HEALEY ALS Platform Trial has demonstrated robust enrollment rates and high data quality despite widespread restrictions caused by the pandemic. These results were achieved through a focused set of protocol changes, as well as close communication with industry partners, trial sites, and the patient community. Lessons from the COVID-19 pandemic can be leveraged to increase access, operational feasibility, and quality of ALS clinical trials long term.

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CLT-10 Relationship between quantitative strength changes and functional outcomes in the Phase 2 FORTITUDE-ALS Trial

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Background: Functional status in patients with ALS as assessed by the ALS Functional Rating Scale-Revised (ALSFRS-R) is the most commonly used primary outcome in Phase 3 clinical trials. While muscle strength loss is intrinsic to decline in function, the specific relationships of strength in individual muscles or muscle groups to functional state are not well described.
Objectives: To evaluate the relationship of alterations in individual or grouped muscle strength to changes in specific domains of the ALSFRS-R.
Methods: FORTITUDE-ALS was a phase 2, double blind, placebo controlled 3-month trial of reldesemtiv in ALS. The ALSFRS-R was measured throughout the trial, and strength was measured using hand-held dynamometry (HHD) in 3 upper extremity muscles (first dorsal interosseous, wrist extensors and biceps) and 3 lower extremity muscles (tibialis anterior, quadriceps, and hip flexors) bilaterally. The ALSAQ-5 was also obtained. We correlated the change in the fine motor domain of the ALSFRS-R (FMD), the gross motor domain (GMD), as well as items 1 (standing) and 2 (using arms) of the ALSAQ-5 to individual upper and lower extremity muscle strength measurements, as well as averages of upper and lower extremity strength.
Results: The ALSAQ-5 item of activities of daily living and independence was well correlated with strength in all upper extremity muscles (Spearman's correlation coefficients (SCC) ranging 0.6–0.7), while ALSAQ-5 item of physical mobility had moderate correlation with lower extremity muscle strength (SCC: 0.4–0.6). The ALSFRS-R FMD had a strong association with First Dorsal Interosseus, Wrist Extensors and Elbow Flexion strength (SCC:0.6–0.7). In the legs, the gross motor domain also had a somewhat strong correlation with Ankle Dorsiflexion and Hip Flexion (SCC 0.6) but the correlation was moderate with Knee Extension (SCC: 0.5). Moderate correlations were also found between the fine and gross motor domains of the ALSFRS-R with SCC of 0.5.
Discussion: Overall, strength and function as measured by both ALSFRS-R and ALSAQ-5 were better correlated in the upper extremity than in the lower extremity. In general, averaging upper and lower extremity muscle strength resulted in higher correlations than single muscle groups. Beyond being an objective and quantitative measure of ALS progression, strength as measured using HHD is moderately to strongly related to functional capacity in ALS.

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CLT-11 Design of FOCUS-C9, an adaptive Phase 1b/2a randomized controlled trial of WVE-004 in patients with C9orf72-associated ALS or FTD

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Hexanucleotide (G4C2)-repeat expansions found in the C9orf72 gene are one of the most common genetic causes of the sporadic and inherited forms of Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD). The discovery that these diseases share a common cause has led to the realization that C9orf72-ALS/FTD is a single genetic disorder that manifests across a clinical spectrum. WVE-004 is an investigational stereopure oligonucleotide that is designed to target C9orf72 transcripts containing the hexanucleotide-repeat expansion and has potential as a disease-modifying therapy for patients with C9orf72-ALS/FTD. WVE-004 contains Wave's new PN chemistry, which has been shown to improve the pharmacological profile of oligonucleotides in preclinical studies. This adaptive Phase 1b/2a study of WVE-004, named FOCUS-C9, is a global, multicenter, randomized, double-blind, placebo-controlled trial that is planned to enroll approximately 50 patients who have a documented hexanucleotide-repeat expansion in C9orf72 and a diagnosis of ALS, FTD, or mixed phenotype. In FOCUS-C9, we will assess the safety and tolerability of single- and multiple-ascending doses of WVE-004 administered intrathecally (IT) by lumbar puncture. Secondary objectives include studying pharmacokinetics (PK) in plasma and cerebrospinal fluid (CSF) and poly glycine-proline (poly-GP) in CSF, a biomarker of pharmacodynamic (PD) effect. Exploratory objectives will consist of assessing changes in biomarkers of neurodegeneration, such as neurofilament light chain (NfL) in the CSF, as well as functional measures, such as ALSFRS-R (Revised ALS Functional Rating Scale), FVC (forced vital capacity), and FTLD-CDR (Frontotemporal Lobar Degeneration-Modified Clinical Dementia Rating). FOCUS-C9 is designed to be adaptive, using PK, PD, safety, and tolerability information to optimize dose level and frequency for each cohort in the single- and multiple-ascending dose phases of the trial. This first-in-human study will evaluate WVE-004 as a potential treatment for C9orf72-associated ALS and FTD.

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CLT-12 Detectable Effect Cluster (DEC) analysis: a novel machine-learning subgroup analysis method for drug rescue

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Introduction: ALS drug development is plagued by high clinical trial failure rates. Subgroup analysis is a key tool used to account for patient heterogeneity, but current methods fall short. DEC analysis systematically groups and analyzes patients based on predicted disease path, creating more homogeneous patient subgroups with reduced noise around the endpoint.
Methods: To perform DEC Analysis, a multivariate, non-linear machine-learning model trained using PRO-ACT was used to rank order trial participants by predicted disease progression. Fifty initial subgroups were expanded by adjusting prediction thresholds in 2% nearest-neighbor increments until the FAS was reached. To analyze subgroups, a matrix was plotted in which each block had distinct upper and lower thresholds. A series of analyses were performed to assess variance (RMSE), treatment effect (TE), effect size, and P-value, thus developing a series of heat maps that revealed subgroups with favorable conditions for detecting a significant effect, whether through enhanced TE and/or lowered variance. The method was applied to the Ceftriaxone-ALS and Topiramate-ALS data sets available from the US NINDS.
Results: To focus on the development of DEC analysis, we used the 285 patients in the Ceftriaxone-ALS dataset who remained on study for 1 year. The 2:1 allocation of the full study was retained in this group and included 190 treated and 95 placebo patients, which allowed us to perform an exploratory analysis to generate a hypothesis for testing in a second analysis. We randomly separated the 190 treated patients into two groups, one for the exploratory analysis and a second for hypothesis testing. One-year predictions using our validated percent expected vital capacity model were made for all patients in the dataset. A broad central region, a hot-spot, where moderately progressing patients localized was detected and a subgroup, representing predicted 15–25% 1-year decline in percent expected vital capacity was selected to determine whether the subgroup could be detected in the test set. Examination of the test group confirmed the results of the exploratory analysis. In contrast to ceftriaxone, which had a slightly positive, non-significant TE, the topiramate trial reported a negative TE for the primary endpoint. DEC analysis using decline in ALSFRS-R as the endpoint was performed and failed to see any positive hot-spots. Rather, the TE matrix showed broad zones of negative TEs. This experiment provides a strong negative control for DEC analysis.
Conclusions: DEC analysis organizes trial participants in an unbiased way into homogeneous subgroups:
"Hot-spots" of detectable TEs that could form the basis for a subsequent successful trial are revealed. Numerous ways to implement this approach are envisioned: "rescue" of drugs that failed late-stage clinical development; all-comers trials to identify patients with detectable effects that can be seamlessly expanded into a fully powered trial.

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CLT-13 IC14 in ALS: Expanded Access Program

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Background: IC14 is a chimeric, monoclonal, anti-CD14 antibody that decreases neuroinflammation by improving T-regulatory (T-reg) cell function. A previous trial of ten participants with ALS receiving four doses of IC14 over four days demonstrated initial safety. We designed an intermediate-size EAP of eight participants with ALS receiving IC14 to learn more about safety, pharmacokinetics (PK), and pharmacodynamics (PD).
Methods: Participants receive intravenous infusions of IC14 every two weeks for 75 weeks. Due to the COVID-19 pandemic, some infusions were administered at home or at a local infusion center. We collected safety labs, amyotrophic lateral sclerosis function rating scale revised (ALSFRS-R), slow vital capacity (SVC), and physical, neurologic, and ophthalmologic exams. Whole blood and serum were collected to determine CD14 receptor occupancy (measured in real time), soluble CD14, and anti-drug antibodies (ADA). Ex-vivo T-reg function and characterization assays were collected starting with the fifth participant.
Results: Average age was 60.2 (±7.7) years, with symptom onset to screening being 19.7 (±10.4) months. Average ALSFRS-R and SVC score at screening was 33.1 (±9.8) and 73.6% (±22.3), respectively. Participants received IC14 up to 59 weeks (average exposure: 40.7 weeks, range: 28–59 weeks). Three participants died due to disease progression. The most commonly reported adverse events (AEs) were falls ($n = 17$) and headaches ($n = 10$); all deemed unrelated to IC14. Treatment-emergent AES (TEASs) deemed probably related to IC14 were tongue paresthesias ($n = 1$) and systemic exhaustion ($n = 1$). There were eleven treatment unrelated serious adverse events (SAEs), the most common being: pneumonia ($n = 2$) and worsening dysphagia ($n = 2$). There were no significant changes in vital signs, exams, or safety labs. Monocyte CD14 receptor occupancy (% RO) increased for all participants after infusion with IC14. RO of greater than 80% was achieved in five participants after one ($n = 2$), two ($n = 1$), or three doses ($n = 2$). One patient required a more frequent dosing regimen (every 10 days) to achieve >80% RO. We also observed an increase in T-reg suppression activity from baseline: 31.9–63.4% over six doses in one participant and 22.1–55.1% in twenty-six doses in another. There were no sustained ADA levels detected out to 41 weeks.
Conclusion: In this intermediate-size EAP, chronic IC14 infusions were safe with no significant changes in laboratory tests, vital signs or ophthalmologic examinations when administered for up to 59 weeks. IC14 was successfully administered at home during the COVID-19 pandemic. TEAEs

were uncommon, mild, and self-limited. Measuring RO in real time for each patient guided the adjustment of dosing frequency. Preliminary but encouraging data suggest an effect on T-reg function. Data collected in this EAP helped inform dosing frequency, however, additional studies will be required to determine a more general and optimal IC14 dose to achieve desired levels of RO (e.g. >90%).

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CLT-14 RESCUE-ALS Trial: a Phase 2, randomized, double-blind, placebo-controlled study of CNM-Au8 to slow disease progression in amyotrophic lateral sclerosis

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Background: RESCUE-ALS is a Phase 2 clinical trial investigating the novel cellular energetic catalyst, CNM-Au8, in patients with recently diagnosed sporadic ALS. CNM-Au8 is an aqueous suspension of highly faceted, clean-surfaced, gold nanocrystals shown to enhance neuronal metabolic energy, reduce oxidative stress, and improve protein homeostasis.
Objectives: To determine the therapeutic effects of orally administered CNM-Au8 as assessed by electromyography (motor unit number index (MUNIX)), a sensitive, quantitative measure of motor unit loss, in a cohort of sporadic ALS patients after 36 weeks of treatment.
Methods: This is a multi-center, randomized, double-blind, parallel group, placebo-controlled study of the efficacy, safety, pharmacokinetics, and pharmacodynamics of CNM-Au8 in early ALS patients. Participants were randomized 1:1 to receive 30 mg of CNM-Au8 or matching placebo once daily over a 36-week double-blind treatment period. Efficacy was assessed as the change from baseline in the MUNIX score summated from for the abductor digit minimi, abductor pollicis brevis, tibialis anterior, and biceps brachii (primary endpoint), and the % predicted forced vital capacity change (secondary endpoint). Exploratory endpoints include additional electromyography assessments (Neurophysiology Index (NPi), Split Hand Index (SHi), MScanFit MUNE), ALSFRS-R, biomarkers, safety, and quality of life assessments.
Results: The trial enrolled 45 participants. Baseline characteristics include [mean (SD)], MUNIX(4)sum score: 378.5 (175.6); FVC % predicted: 81.5 (16.7); ALSFRS-R: 38.7 (6.0); mean time from diagnosis to randomization: 3.6 (2.7) months; mean time from symptom onset to randomization: 16.7 (9.7) months; riluzole background treatment: 89%; ENCALS risk score: −4.6 (1.8). Analyses of the change in the MUNIX(4)sum score from baseline to either week 12 or week 24 of the overall study population (active and placebo) significantly correlated with, and predicted, the change from baseline to end of study (week 36) for both the ALSFRS-R score as well as the FVC (% predicted). Unblinded efficacy (e.g., summated MUNIX score, FVC (% predicted), ALSFRS-R, NPi, SHi), and safety data will be presented.
Discussion: As the first catalytic nanocrystal in development for the treatment of neurodegenerative diseases, CNM-Au8 has a unique multi-modal mechanism of action that addresses ALS disease-related cellular energetic failure, oxidative stress, and proteostasis dysregulation. Final results from this study will determine whether targeting the treatment of energetic failure with CNM-Au8 is a valid therapeutic approach to slow ALS disease progression. This study further supports the validation of neurophysiological endpoints as disease-relevant biomarkers of ALS disease progression.

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CLT-15 Update of COURAGE-ALS: a Phase 3, double-blind, randomized, placebo-controlled, study to evaluate efficacy and safety of reldesemtiv in patients with ALS

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Background: Reldesemtiv is a selective small molecule fast skeletal muscle troponin activator that sensitizes the sarcomere to calcium by increasing the affinity of troponin for calcium. In FORTITUDE-ALS, a phase 2 trial, key eligibility criteria were time from diagnosis of ALS ≤24 months and slow vital

capacity (SVC) ≥ 60% of predicted. The primary analysis of the change in SVC from baseline to Week 12 did not reach statistical significance. However, positive trends were noted in SVC, ALSFRS-R, and muscle strength. Post hoc post-hoc analyses suggested that treatment effects were carried more strongly in patients with shorter symptom duration and faster pre-study ALSFRS-R progression rates. These observations informed the design of the ongoing phase 3 trial of reldesemtiv in ALS.

Objectives: To evaluate the effect of reldesemtiv versus placebo on functional outcomes and a joint rank test of function, respiratory insufficiency and survival in patients with ALS.

Methods: Key inclusion criteria for the Phase 3 double-blind, randomized, placebo-controlled COURAGE-ALS trial (Clinical Outcomes Using Reldesemtiv on ALSFRS-R in a Global Evaluation in ALS include symptom onset within 24 months, ALSFRS-R score of ≤44 and upright forced vital capacity (FVC) ≥ 65% of predicted for age, height and sex. Approximately 555 participants will be randomized 2:1 to reldesemtiv 300 mg BID or placebo for 24 weeks; all patients then receive reldesemtiv for an additional 24 weeks. Stable doses of riluzole and or edaravone are permitted; patients are stratified accordingly. The primary endpoint is change from baseline in the ALSFRS-R total score at 24 weeks. Secondary endpoints include the combined assessment of ALSFRS-R total score, time to onset of respiratory insufficiency and survival time up to Week 24 using a joint rank test, change from baseline to 24 weeks in FVC, ALSAQ-40, and bilateral handgrip strength. To reduce patient burden, approximately half of the study visits will be performed remotely. COURAGE-ALS is currently being conducted in North America, Australia, and Europe.

Results: Demographic features and baseline ALS related characteristics of the randomized cohort to date will be presented and compared to FORTITUDE-ALS.

Discussion: COURAGE-ALS is an ongoing phase 3 trial of reldesemtiv in ALS incorporating inclusion criteria designed to enrich the patient population to those whose disease course trends toward moderate to more rapid progression rates to increase the sensitivity of detecting a treatment effect. We anticipate that this trial will provide clear evidence as to whether a fast skeletal troponin activator can have a meaningful role in the treatment of patients with ALS.

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CLT-16 Clinical trial of bosutinib for amyotrophic lateral sclerosis: induced pluripotent stem cell-based drug repurposing for amyotrophic lateral sclerosis medicine (iDReAM) study

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Background: Amyotrophic lateral sclerosis (ALS) is a progressive, severe neurodegenerative disease caused by the loss of motor neurons. There have as yet been no fundamental curative medicines for ALS, and the development of an effective medicine is urgently required. Induced pluripotent cell (iPSC)-based drug repurposing identified a Src/c-Abl inhibitor, bosutinib, as a candidate for molecular-targeted therapy of ALS. Bosutinib is a selective inhibitor of Src/c-Abl tyrosine kinase, and is approved for the treatment of chronic myelogenous leukemia (CML).

Methods: A Phase 1, open-label, multi-center, 3 + 3 dose escalation study was conducted to evaluate the safety and tolerability of bosutinib for ALS patients. The preliminary efficacy of bosutinib was also evaluated using the clinical score of ALS Functional Rating Scale-Revised (ALSFRS-R), and predictive biomarkers were explored. The study consisted of a 12-week observation period, a 1-week transitional period, a 12-week study treatment period, and a 4-week follow-up period. After completion of the transitional period, subjects whose total ALSFRS-R score decreased by 1–3 points during the 12-week observation period received bosutinib for 12 weeks. Successive cohorts of patients received escalating doses of bosutinib starting from 100 mg QD (quaque die) up to 400 mg QD based on dose limiting toxicity (DLT) occurrence in the first 4 weeks of bosutinib treatment.

Results: A total of 20 participants were enrolled, 13 of whom received bosutinib treatment, and 12 were included in the safety and efficacy analyses. No DLTs were observed up to 300 mg QD, but three DLTs (two cases of Grade 3 aspartate and alanine aminotransferase increase, one case of disseminated erythematous papular) were observed in the 400 mg QD cohort. The safety profile was consistent with what is known for CML treatment, and neither new safety signals nor ALS-specific adverse events were observed. Although the study was conducted with a small number of cases, bosutinib administration was found to halt progression in some of the participants, and 5 of 9 patients who had completed the administration of scheduled doses of bosutinib showed stable disease. Furthermore, a biomarker was found to enrich the target population showing a strong drug effect.

Conclusions: This study showed that bosutinib administration up to 300 mg QD was safe and well tolerated, with promising efficacy for motor symptoms in ALS. (Funded by AMED; ClinicalTrials.gov number, NCT04744532)

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CLT-17 MERIDIAN: a phase 2, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of pegcetacoplan in patients with amyotrophic lateral sclerosis

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Background: Inflammation is a key feature underlying the pathogenesis of numerous neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS). In ALS, the complement system has been implicated in neuropathology and disease progression. Pegcetacoplan is a subcutaneously administered C3 complement inhibitor that is being investigated in hematology, nephrology, and neurology. The current clinical study (NCT04579666) is investigating whether attenuating C3 activity can improve survival and function in people diagnosed with apparent sporadic ALS.
Objectives: Determine the efficacy and safety of pegcetacoplan compared to placebo among people diagnosed with ALS in a global, multicenter, randomized, double-blind, placebo-controlled, phase 2 study.
Methods: Approximately 228 patients diagnosed with apparent sporadic ALS, ≥18 years of age and with an ALS Functional Rating Scale-Revised (ALSFRS-R) score ≥30, slow vital capacity (SVC) ≥ 60% of the predicted value at screening, and with symptom onset within 72 weeks prior to screening, are eligible for enrolment. Following screening, patients will be randomized 2:1 to treatment groups receiving either subcutaneous pegcetacoplan (1080 mg) or placebo twice weekly for a duration of 52 weeks. The primary efficacy endpoint is the difference in the Combined Assessment of Function and Survival (CAFS) ranked score at 52 weeks after treatment initiation. Additional, secondary functional efficacy (ALSFRS-R, percent SVC, muscle strength, quality of life, and caregiver burden) and safety endpoints will be analyzed at 52 weeks. Following the placebo-controlled period, all patients will have the option to receive pegcetacoplan in an open-label period for an additional 52 weeks.
Results: This ongoing study is currently enrolling participants.
Conclusions: Results of this study will determine the role of complement and C3 inhibition in patients with ALS.

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CLT-18 Factors influencing trial participation in motor neuron disease (FIT-Participation in MND)

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Background: The Motor Neuron Disease Systematic Multi-Arm Randomised Adaptive Trial (MND-SMART) is a multi-site United Kingdom clinical trial seeking to address the paucity in effective disease modifying drugs for people with motor neuron disease (pwMND). Historically, MND trials have been plagued by suboptimal recruitment and high rates of attrition. Failure to recruit and/or retain trial participants can result in insufficiently representative samples, terminated trials, or invalid conclusions.
Objectives: This study seeks to investigate patient-specific factors that affect recruitment and retention to MND-SMART. An understanding will improve trial design, optimising recruitment and minimise attrition. We hypothesise patient-specific factors (neuropsychiatric symptoms, cognitive impairment, behavioural change, disease phenotype, quality of life, and physical functioning) will have a significant impact upon pwMND's decision to participate and remain in, MND-SMART.
Methods: Participants were recruited from the Scottish MND Register, Clinical Audit Research and Evaluation MND (CARE-MND). A comprehensive suite of questionnaires was administered (online or paper versions), including Hospital Anxiety and Depression Scale, Patient Health Questionnaire and State-Trait Anxiety for neuropsychiatric symptoms, ALS-Specific Quality of Life and attitudes to trials. Caregivers were invited to complete the Brief Dimensional Apathy Scale. Clinical data relating to phenotype, demographics, Edinburgh Cognitive Assessment Screen, ALS Functional Rating Scale and prior research involvement were extracted from CARE-MND and MND-SMART databases. Descriptive statistics will be used to summarise questionnaire responses, compare scores between variable groupings and report participants reaching pre-defined impairment thresholds for cognitive, behavioural and neuropsychiatric. To explore the association of covariates with trial engagement we will use logistic regression modelling. The binary outcomes of participation versus non-participation, and current participation versus withdrawal, will best explored using regression to evaluate the impact of the exploratory covariates on trial involvement. Results will be presented as odds ratios and with 95% confidence intervals.
Results: 158 pwMND consented to participate with 120 completing questionnaires, 10 individuals died prior to completing. 5% chose telephone appointments, remaining responses split equally between online and paper. Additional behavioural questionnaire completed by caregivers in 73% of

respondents. Participants were 67% male, mean age 66 years (range 39–85) and 58% amyotrophic lateral sclerosis sub-type of MND. 40% of participants had participated in additional research projects prior to FIT-Participation-MND. 40% are in MND-SMART, expected to increase as more sites across Scotland become established.
Discussion: This is the first study to prospectively explore pwMND's reasons for joining, and remaining, in a clinical trial. Recruitment is now complete, with a quarter of the Scottish MND population completing questionnaires. After 12 months, we will assess how many people in this study were recruited into the trial and how many remain involved. Ethical approval was provided by the West of Scotland Research Ethics Committee 3 (20/WS/0067) on 12th May 2020.

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CLT-19 A French national network to improve organization and inclusion in clinical trials: alliance on Clinical Trials for ALS-MND (ACT4ALS-MND)

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Background: In France, specialized multidisciplinary ALS care is provided by 19 dedicated ALS/MND centers accredited by the Directorate of Health Care Supply of the French Ministry of Health (DGOS). More than 8 out of 10 French patients with ALS or other MND are followed up quarterly in one of these centers with an active ALS patient population around 6000 cases and 1500 new cases per year (1). Efficient national coordination is ensured by a specialized network managed and funded by the DGOS, the "Filière de Santé Maladies Rares FilSLAN", which acts as a link and oversees the actions between the different stakeholders involved in ALS and MND care to guarantee homogenous professional practices, and also provides assistance in the development and structuring of clinical research.
Objectives: To describe the implementation and functioning of the FilSLAN French national network ACT4ALS-MND which was created in 2020 to facilitate and dynamize French clinical research in the field, and specifically increase the number of clinical trials and rate of inclusion of French ALS centers.
Methods: ACT4ALS-MND brings together expertise of the 19 expert centers in the field throughout France. It was set up following the French label for Clinical Research Infrastructure network "FCRIN" requirements specifications with effective governance and operational processes based on an executive board and a steering committee, with the support of a full-time project manager.
Results: ACT4ALS-MND ensures a centralized access to its centers and provides operational support for all steps of a research project: scientific expertise and methodological support for trial design, regulatory expertise, feasibility study and site selection, financial evaluation, initiations in the centers and recruitment follow-up. The network's action is underpinned by implementation of a French national database on ALS/MND (≃16,000 patients prospectively followed-up) and a specific additional form for data collection in the French national rare diseases database, to gain access in real time for each center to the main phenotypic and biological data required for clinical trials selection criteria. ACT4ALS-MND ensures an active link with the European clinical research consortium TRICALS (Treatment and Research Initiative to Cure ALS). To date, the network is leading or contributing in 7 academic-funded projects (2 European grants), and 10 industrially-sponsored trials.
Discussion: Built on close interactions between 19 French expert ALS centers with a large active patient population and leading basic science teams in the field, ACT4ALS-MND aims to be an interface for transversal dialogue between academic research and industry, for removing administrative and regulatory obstacles in order to accelerate the availability of innovations for French ALS and MND patients.

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Reference

1. Couratier P, Corcia P, Lautrette G, et al. Rev Prat. 2016;66: 556–8.

CLT-20 Long-term survival analysis from Masitinib early access named patient program

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Background: Masitinib administered at 4.5 mg/kg/day as an add-on to riluzole has previously demonstrated a positive benefit–risk balance in ALS patients with an ALSFRS-R progression rate from disease-onset to baseline (ΔFS) of <1.1 points/month (study AB10015) (1). Recently reported long-term survival data from that study showed that masitinib 4.5 mg/kg/day could prolong survival by over 2 years and reduce risk of death by at least 44% as compared with placebo, provided that treatment starts early in disease (i.e. prior to severe impairment of functionality) (2).
Objective: We report on a subgroup long-term survival analysis based on masitinib's early access Named Patient Program (NPP).
Methods: Following data readout for the main protocol period of study AB10015, treatment assignment was unblinded and an optional, open-label, early access NPP was initiated. This NPP permits comparison between patients randomized to the masitinib treatment-arms (4.5 or 3.0 mg/kg/day) of study AB10015 who continued to receive masitinib treatment under the NPP (referred to as the 'NPP-M4.5' and 'NPP-M3.0' cohorts, respectively, with a pooled cohort designated as 'NPP-M[pooled]'), against those patients from the placebo (PBO) arm that did not participate in the NPP and were therefore never treated with masitinib (referred to as the 'masitinib-naïve PBO' cohort). Patients who had died prior to NPP initiation (01 November 2017) were excluded. Survival status of all patients originally randomized in AB10015 was collected from participating investigational sites. Survival analysis was performed via the multivariate log-rank test and Cox proportional-hazards model.
Results: The cohorts of 'NPP-M4.5', 'NPP-M[pooled]' and 'masitinib-naïve PBO' comprised 29, 59, and 53 patients, respectively. Assessment of baseline imbalances showed no indication of self-selection bias. Kaplan-Meier survival curves visually showed divergence between NPP subpopulations and the placebo comparator arm, indicating a consistent survival advantage in favor of masitinib. Survival was significantly prolonged by 11 months in the 'NPP-M4.5' cohort relative to 'masitinib-naïve PBO' (median OS of 73 (95%CI[69–NE]) versus 62 (95%CI[49–NE]) months, respectively, $p = 0.008$), with a significant 67% reduced risk of death (Hazard Ratio 0.33 (95%CI[0.12–0.88]); $p = 0.027$). Likewise, survival was significantly prolonged (11 months, $p = 0.008$), for the 'NPP-M[pooled]' cohort relative to 'masitinib-naïve PBO', despite an inevitable dilution from 'NPP-M3.0' patients, with a 42% reduced risk of death (0.58 (95%CI[0.28–1.19]); $p = 0.134$).
Discussion: This analysis effectively avoids confounding effects related to treatment switch-over (i.e. placebo patients switching to masitinib). NPP long-term OS analysis showed a significant survival advantage in favor of masitinib-treated patients as compared with masitinib-naïve patients. This benefit is consistent with results from long-term OS analysis of the overall study population, even in the absence of patient enrichment.

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References

1. Mora JS, Genge A, Chio A, et al. Amyotroph Lateral Scler Frontotemporal Degener. 2020;21(1–2):5–14.
2. Mora JS, Bradley WG, Chaverri D, et al. Ther Adv Neurol Disord 2021;14:1–16.

CLT-21 Global Phase 3, randomized, placebo-controlled trial of a fixed-dose coformulation of sodium phenylbutyrate and taurursodiol in amyotrophic lateral sclerosis (A35-004 PHOENIX): study design overview

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Background: An oral, fixed-dose coformulation of sodium phenylbutyrate (PB) and taurursodiol (TURSO) was designed to attenuate neuronal death by simultaneously targeting endoplasmic reticulum and mitochondrial dysfunction. The safety and efficacy of PB/TURSO were evaluated in adults with definite ALS (revised El Escorial criteria [rEEC]) ≤ 18 months from symptom onset with slow vital capacity (SVC) > 60% in the phase 2 CENTAUR trial comprising a 24-week randomized period and up-to-132-week open-label extension period. PB/TURSO was associated with significantly slower functional decline in the randomized period of CENTAUR, and overall survival (OS) was significantly longer in those starting on PB/TURSO versus placebo at nearly 3 years after randomization. Similar adverse event (AE) rates were observed with PB/TURSO and placebo in the randomized period.

Objective: To describe the design of a phase 3 trial assessing safety and efficacy of PB/TURSO in a broader, international population of people with ALS.
Methods: PHOENIX will be conducted in approximately 55 Treatment Research Initiative to Cure ALS (TRICALS) and Northeast ALS Consortium (NEALS) sites in Europe and the United States and include 600 participants (EU, $n \approx 400$; US, $n \approx 200$). Inclusion criteria expand on those in CENTAUR to enroll adults with clinically probable as well as definite ALS (rEEC), SVC $\geq$55%, and symptom onset $<$24 months prior to randomization. Participants will be randomized 3:2 to receive PB/TURSO (3 g PB/1 g TURSO per sachet) or matching placebo by mouth or feeding tube, 1 sachet per day for approximately 14–21 days and then, if tolerated, 1 sachet twice a day for the remainder of the 48-week study. Participants who complete the 48-week study will have the option to receive PB/TURSO after the trial if permitted by each region's regulatory guidance. This posttrial access to PB/TURSO will also be dependent on regulatory and reimbursement milestones.
Results: Safety assessments will include incidence and severity of AEs and trial discontinuations. The primary efficacy outcome is a joint assessment of ALS Functional Rating Scale–Revised total score progression over 48 weeks and survival. Secondary efficacy outcomes include changes from baseline in SVC and patient-reported quality of life and health status outcomes (ALSAQ-40, EQ-5D, and EQ VAS); time to transition through King's and MiToS stages; ventilation-free survival rates; and OS, with all-cause mortality assessed beyond the planned 48-week follow-up. Exploratory outcomes include caregiver burden and measurement of plasma drug exposure and biomarkers of neuron damage and neuroinflammation.
Discussion: Phase 3 PHOENIX trial of PB/TURSO in ALS will build on findings of the phase 2 CENTAUR trial by incorporating a larger, global, and more heterogeneous population of people with ALS followed for a longer duration. Early data relating to enrollment are expected to be available in late 2021.

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CLT-22 PrimeC as a novel therapeutic strategy for ALS treatment

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Background: ALS has a complex underlying pathophysiology in which multiple pathways are involved, such as dysregulation of microRNA metabolism, iron accumulation and neuroinflammation (1). Dysregulated microRNAs are found in ALS models' and in patient's microglia cells, motor neurons and skeletal muscles. microRNAs control multiple molecular mechanisms such as neuroinflammation, synaptic formation, neuronal activity and differentiation (1). Increasing evidence suggests that chronic neuroinflammation, characterized by microglia activation and secretion of proinflammatory cytokines as well as accumulation of brain iron, are hallmarks of ALS (1). Since the many pathological pathways of ALS are clearly convoluted and complex, a multi-factorial strategy is needed in order to target multiple pathways simultaneously and synergistically.
PrimeC is a novel combined formulation composed of unique doses of Ciprofloxacin and Celecoxib, which aim to synergistically inhibit the progression of ALS by addressing these three aforementioned pathologies.
In addition to being a broadly used fluoroquinolone antibiotic, ciprofloxacin is a potent iron chelator, as well as a regulator of Dicer activity, a key enzyme in the microRNA processing pathway. It can also indirectly hinder neuroinflammation (1). Celecoxib, an NSAID, regulates neuroinflammation mainly through COX-2 inhibition. Additionally, it has COX-2-independent anti-inflammatory activities. Although celecoxib has not historically shown benefit for ALS patients when given at high doses as a single agent (2), preclinical studies in ALS models showed a synergistic effect when combined in low doses with ciprofloxacin (1).
Objective: This study aimed to evaluate the safety and tolerability of PrimeC, and to examine its effects on ALS-related biomarkers
Methods: PrimeC has been evaluated clinically in a 12-month, open-label, phase IIa study in 15 patients with ALS.
Results: Results demonstrate that PrimeC was found to be safe and tolerable in the ALS patient population. These findings were reinforced by several virtual models (i.e Origent and ENCALS prediction models, and matched patients from the PRO-ACT database), which showed no safety concerns with regards to patient adverse events and survival. Additionally, the effect of PrimeC on serum neurofilament levels, as well as on neuronal extracellular vesicle (EVs) key ALS-related biomarkers was examined by extracting EVs from patient serum samples. Results exhibited significant change in exosomal-TDP-43 following PrimeC treatment, accompanied by a similar effect on the key autophagy marker LC3.
Discussion: The present study demonstrates that PrimeC is safe and well-tolerated. Of significance, all patients completing the trial have opted to continue into an extension study with PrimeC.
These safety findings in conjunction with the biological activity observed in biomarkers analysis, set the stage for a larger, placebo-controlled, pivotal study to examine the efficacy of PrimeC in ALS treatment.

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References

1. Goldshtein H, Muhire A, Petel Légaré V, et al. Efficacy of ciprofloxacin/celecoxib combination in zebrafish models of amyotrophic lateral sclerosis. Ann Clin Trans Neurol. 2020;7:1883–97.
2. Cudkowicz ME, Shefner JM, Schoenfeld DA, et al. Trial of celecoxib in amyotrophic lateral sclerosis. Ann Neurol. 2006;60:22–31.

CLT-23 Interim results from the MT-1186-A01 Phase 3, open-label, multicenter safety study of oral edaravone administered over 48 weeks in subjects with amyotrophic lateral sclerosis

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Background: Radicava® (edaravone) is a US Food and Drug Administration-approved treatment for ALS that has been shown to slow the rate of physical functional decline (1,2) There is interest in a nonintravenous (non-IV) formulation of edaravone and an ongoing, multicenter phase 3 study is currently assessing the safety and tolerability of an investigational oral formulation of edaravone (MT-1186).
Objective: To assess the long-term safety and tolerability of investigational oral edaravone in patients with ALS.
Methods: This global, multicenter, open-label phase 3 study is evaluating the long-term safety and tolerability of investigational oral edaravone in patients with ALS. The study includes a screening period of up to 3 weeks, an open-label treatment period of 48 weeks, and a safety follow-up period of 2 weeks after the last dose. Entry criteria include males and females aged $\geq$18 years to 75 years, with an ALS diagnosis of definite ALS, probable ALS, probable laboratory-supported ALS, or possible ALS, according to El Escorial criteria; baseline forced vital capacity $\geq$70% predicted; disease duration $\leq$3 years; and functioning independently.
Patients are receiving a 105-mg dose of investigational oral edaravone administered in treatment cycles that replicate the dosing of IV edaravone. This includes an initial treatment cycle with daily oral dosing for 14 days, followed by a 14-day drug-free period. Subsequent treatment cycles consist of daily oral dosing for 10 days of a 14-day period, followed by a 14-day drug-free period. Treatment cycles are every 4 weeks.
In addition to the primary safety analysis, the study also includes exploratory end points, such as change from baseline in the revised ALS Functional Rating Scale (ALSFRS-R) score and time to death, tracheostomy, or permanent assisted mechanical ventilation.
Results: A total of 185 patients were enrolled in the MT-1186-A01 study, with a mean age of 59.9 years. Fifty-eight percent of the patients are Caucasian and 35% are Japanese. The baseline mean score for the ALSFRS-R was 40. Additional baseline characteristics and interim data after 24 weeks of treatment will be included in the poster presentation.
Discussion: The first phase 3 trial of investigational oral edaravone will provide important information on the long-term safety and tolerability of this new formulation of edaravone in patients with ALS.

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References

1. RADICAVA® (edaravone) [package insert]. Jersey City, NJ: Mitsubishi Tanabe Pharma America, Inc; 2021.
2. Writing Group; Edaravone (MCI-186) ALS 19 Study Group. Lancet Neurol. 2017;16(7):505–12.

CLT-24 A randomized, open-label, crossover-design, single-dose Phase 1 study to investigate the safety, tolerability, and comparative bioavailability of investigational oral edaravone administered orally and via a nasogastric tube in healthy adult subjects (MT-1186-Z-101)

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Background: Radicava® (edaravone injection) is a US Food and Drug Administration–approved treatment for ALS that has been shown to slow the rate of physical functional decline (1,2). As intravenous administration can burden patients, orally administered treatments are needed. Some ALS patients may undergo a percutaneous endoscopic gastrostomy (PEG) for required nutritional and medical support due to dysphagia as ALS progresses. The possibility of administering drugs to ALS patients via a PEG tube should be considered.
Objective: To assess the comparative bioavailability and pharmacokinetics (PK) of an investigational oral suspension formulation of edaravone (MT-1186) when administered with a nasogastric feeding tube as a model of administration via a PEG tube.
Methods: Study Z-101 is a randomized, open-label, crossover-design, single-dose phase 1 study (3). The primary objective of the study is to investigate the comparative bioavailability of MT-1186 administered orally and via a nasogastric tube in healthy adult subjects. Administration via nasogastric feeding tube was used as a way of modeling a PEG tube because both are positioned in the stomach, are similar in composition, and are compatible with an oral suspension of edaravone, and because only administration via nasogastric feeding tube is feasible in healthy adults. Secondary objectives include assessing the safety, tolerability, and PK. Subjects will receive a single dose of MT-1186 and PK will be assessed over 48 h, followed by crossover to the other form of administration. Safety assessments were also conducted during the study.

Results: A total of 36 subjects were randomized to two groups of 18 subjects. Study results will be presented on the poster.
Discussion: This study should provide important data for the development of MT-1186 for patients with ALS who are administered with MT-1186 through a PEG tube or intragastrically.

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References

1. RADICAVA® (edaravone injection) [package insert]. Jersey City, NJ: Mitsubishi Tanabe Pharma America, Inc; 2021.
2. Writing Group; Edaravone (MCI-186) ALS 19 Study Group. Lancet Neurol. 2017;16(7):505–12.
3. ClinicalTrials.gov listing. Available at: https://clinicaltrials.gov/ct2/show/NCT04776135. Accessed July 29, 2021.

CLT-25 Efficacy and safety of RIPK1 inhibitor SAR443820 in adult participants with amyotrophic lateral sclerosis (ALS): phase 2 study design

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Background: Receptor-interacting serine/threonine-protein kinase 1 (RIPK1) is an intracellular protein involved in regulating inflammation, cytokine release, and cell death. In amyotrophic lateral sclerosis (ALS) pathophysiology, RIPK1 critically mediates necroptosis and inflammatory pathways. SAR443820 is a selective, orally bioavailable, central nervous system penetrant, reversible inhibitor of RIPK1. By inhibiting necroptosis and inflammatory signalling through RIPK1, SAR443820 has the potential to modify the course of ALS. ACT16970 is a phase 2 study that will determine the efficacy and safety of SAR443820 in people with ALS.
Objective: To present the study design of ACT16970
Methods: This is a multicenter, randomized, double-blind, placebo-controlled study followed by a long-term extension period. The study will include adults aged 18–80 years with diagnosis of possible, clinically probable, clinically probable laboratory-supported, or definite ALS, with disease duration $\leq$2 years and respiratory function SVC $\geq$60% at screening. The study will include approximately 230 participants. ACT16970 includes a placebo-controlled period (Part A) and an open-label period (Part B). Part A is a 24-week, double-blind, placebo-controlled treatment period where study participants will be randomized in 1:1 ratio to receive either oral SAR443820 or placebo. The primary endpoint of Part A is the rate of decline from baseline in the revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) total score over 24 weeks. Part B is a 2-year open-label, long-term extension that will begin at end of Week 24 and proceed through Week 128, where every participant will receive SAR443820. The primary goal of Part B is to assess the long-term efficacy and safety of SAR443820 in people with ALS.
Discussion: ACT16970 study has been designed to assess the effect of SAR443820 compared to placebo in reducing ALS progression as measured by ALSFRS-R. The study is designed with both a randomized, placebo-controlled, double-blind part to generate well-controlled efficacy and safety data, as well as an open-label part to provide longer term efficacy and safety data.

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CLT-26 REALS-1: A randomized, double-blind, parallel group, single centre, phase 1b/2 study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of three orally administered doses of enoxacin in adults with amyotrophic lateral sclerosis

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Background: Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disorder caused by the selective death of motor neurons in the CNS leading ultimately to death within 2–5 years of diagnosis. There are currently no curative therapies for ALS and only two disease-modifying therapies have been approved: Riluzole and Radicava (edaravone).
Much focus has been placed on uncovering the genetic mechanisms that cause ALS. Interestingly, many of the genes in which ALS-causing mutations have been identified code for RNA-binding proteins. It is therefore hypothesized that dysregulation of RNA activity may be involved in the pathogenesis of ALS. microRNAs (miRNAs), which are endogenous, non-protein coding, small RNAs that silence messenger RNA (mRNA) at the post-transcriptional level, are globally downregulated in motor neurons of people with sporadic and familial ALS, as well as in cultured neurons that express ALS-causing mutant forms. Further evidence suggests that this global downregulation of miRNAs in ALS may be the result of impaired Dicer activity. Specifically, in cells transfected with ALS-causing mutant forms of TDP-43, FUS or SOD1, Dicer activity was shown to be significantly reduced. This reduction in Dicer activity could be partially rescued by the presence of enoxacin, a fluoroquinolone antibiotic originally

approved for the treatment of genitourinary tract infections, that has since been identified to increase Dicer activity. In the SOD1G93A mouse model of ALS, enoxacin was shown to delay the deterioration of motor function, when assessed by multiple locomotive and neurological criteria. Additionally, in induced pluripotent stem cells (iPSCs)–derived motor neurons from people with ALS, enoxacin rescued expression of miRNAs that were downregulated relative to iPSC-derived motor neurons from healthy controls. Collectively, these preclinical data suggest that enoxacin has the potential to restore miRNA levels and thereby have a beneficial effect on disease pathogenesis in patients with ALS. This supports testing enoxacin as a disease-modifying therapeutic for ALS.
Objectives: REALS-1 is a randomized, double-blind, parallel group, phase 1b/2 study to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of three orally administered doses of enoxacin (200mg twice daily, 400mg twice daily and 600mg twice daily).
Methods: 36 adult participants with ALS will be randomized 1:1:1 to each treatment arm. The primary outcomes are safety and tolerability as assessed by incidence of adverse events and serious adverse events. The secondary outcome is the PK profile of the three oral doses of enoxacin. Exploratory outcomes include examination of the PD profile of enoxacin, including effects on miRNA expression.
This study will provide evidence around the safety, tolerability, and dosing of enoxacin as a potential therapy for ALS, and represents an important first step in the clinical development of enoxacin for ALS. The study opened for recruitment in March 2021.

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CLT-27 COMBAT-ALS phase 2B/3 trial of MN-166 (IBUDILAST) in ALS: trial update

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Background: MN-166 (ibudilast), an orally available, centrally active small molecule, inhibits macrophage migration inhibitory factor and phosphodiesterases 3,4, and 10, and has well-known anti-inflammatory and neuroprotective properties. Notably, a recent *in vitro* study showed that ibudilast enhanced clearance of disease-linked TDP-43 and SOD1 protein aggregates, thus acting as an autophagy enhancer (1). A completed Phase 1b/2a trial in ALS participants suggested MN-166 slows disease progression more effectively than riluzole alone in certain subgroups of ALS patients and observed higher rates of stability or improvement in ALS functional activity in participants treated with MN-166.
Objectives: The primary objective of the study is to evaluate the efficacy of MN-166 versus placebo on patient's functional activity measured by ALSFRS-R score and survival in ALS participants. Secondary objectives are to evaluate the efficacy on muscle strength measured by hand-held dynamometry, quality of life measured by ALSAQ-5, safety, and tolerability, and to characterize the pharmacokinetics (PK) of MN-166 using population PK modeling.
Methods: This is a Phase 2b/3, multicenter, randomized, double-blind (12 months), placebo-controlled study followed by an open-label extension phase (6 months) compared to matching placebo in participants diagnosed with ALS. Participants who meet entry criteria will be randomly assigned 1:1 to 1 of two treatment groups, up to 100 mg/day MN-166 or matching placebo. We plan to enroll 230 participants at 30 sites in US, Canada, and Europe. (NCT04057898)
Riluzole and edaravone are permitted medications while the participant is taking study drug.
Results: Approximately 20 sites in the US and Canada are actively enrolling participants. The COVID-19 pandemic prevented study enrollment in Europe, however, activity has resumed to open sites in some countries. Enrollment status and baseline characteristics of enrolled participants will be available at the time of final presentation.
Discussion: Major ongoing activities of COMBAT-ALS will be reported.
Please refer to the COMBAT-ALS webinar for more details on MN-166, patient support system (MedACT), and social media sites supporting the trial (2).

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References

1. Chen Y, Wang H, Ying Z, et al. Biochem Biophys Res Commun. 2020;526(1):231–8.
2. https://medicinova.com/medicinova-webinar/

CLT-28 The Morris ALS Principles: amulti-stakeholder framework for patient-driven research

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Background: ALS is a devastating neurodegenerative disease. In the more than 150 years since it was first described, there are still no effective treatments or cures. One of the goals of I AM ALS is to remove barriers to therapies and improve ALS care and research from a multi-stakeholder perspective. Despite their expertise and contributions, people living with and impacted by ALS are still being blocked from attending scientific forums sponsored by organizations that are supposed to be serving the community. As such, ALS advocates turned to the HIV community to learn from how they demanded – and received – seats at the decision-making tables. Inspired by the Denver Principles, a landmark document drafted by HIV/AIDS activists in 1983, ALS advocates sought to create the first guidance document to outline people living with ALS' expectations regarding their inclusion in matters directly affecting them. The Morris Principles serve as a social contract that solidifies the necessary involvement of people living with ALS.
Methods: Advocates met weekly via Zoom and corresponded via email from 5 March 2021 to 21 May 2021 to

define and refine a document in an iterative process inspired by the Delphi consensus method.
Results: Advocates identified five priority areas: (1) protecting "intellectual, physical and financial dignity"; (2) global stewardship of "our disease and respected partners in the science of treatments and cures"; (3) acting as trusted peers with clinicians, researchers, and policy makers; (4) fighting for "equity in decision-making"; and (5) leading to end ALS. Specific guidance was developed for targeted audiences: healthcare professionals; scientific and ALS research community; ALS policy community, legislators and regulators; and ALS nonprofits. This guidance document came to be named the Morris ALS Principles, as it was inspired by ALS advocate Sandy Morris. I AM ALS posted the Morris Principles on their website and allowed people to download a copy. I AM ALS and their community members then distributed the principles to ALS stakeholders. The Morris ALS Principles authors recommend the invocation of the principles in all interactions with stakeholders. The principal developers encourage all stakeholders to use the document when developing programs or initiatives and point out where the principles are not being adhered to. ALS advocates will work with and publicly cite offenders and upholders of the Morris ALS Principles, as well as proactively collaborate with organizations to confirm they are in adherence with the principles.
Conclusion: The Morris ALS Principles provide a multi-stakeholder advocacy framework to create a more ethical and effective ALS landscape. We recommend that all stakeholders who work in the ALS space review, use, and enforce these principles. This will be a living document that will be maintained in the spirit of continuous improvement.

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CLT-29 Biomarker assays utilized in the Radicava/edaravone findings in biomarkers from ALS (REFINE-ALS) study

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Background: A diversity of prognostic, predictive, and pharmacodynamic biomarkers are proposed in ALS, but few have been validated. Radicava® (edaravone injection) gained US FDA approval for treatment of ALS based on its ability to slow decline in physical function. The REFINE-ALS study combines standardized sample collection procedures with optimized biomarker assays to obtain real-world data on a variety of biomarkers in a broad group of people with ALS.
Methods: This prospective, observational, longitudinal, multicenter US study will enroll up to 300 adult patients with ALS who initiate edaravone treatment as a part of their clinical care. Participation after the screening period will continue for approximately 24 weeks, 6 cycles of edaravone, administered according to the FDA-approved dosing regimen.
Biomarker testing and other standard-of-care assessments will be performed at baseline and during on- and off-drug intervals of cycles 1, 3, and 6. Biomarkers of oxidative stress (3-nitrotyrosine, 4-hydroxynonenal, F2 isoprostanes, 8-hydroxy-2′-deoxyguanosine, and urate), inflammation (matrix metalloproteinase-9), neuronal injury and death (phosphorylated heavy and light chain neurofilaments, and urinary neurotrophin receptor p75), and muscle injury (creatinine), epigenetics (EpiSwitch™), and a biomarker discovery panel (SOMAscan®) are being evaluated. DNA samples are collected for genomic sequencing. Trained nurses collect blood and urine samples during study visits to the clinic or at the participant's home. Samples are processed and shipped for same-day delivery to a central collection company on either dry or wet ice as appropriate for the assays being conducted. Samples are stored centrally and later distributed to the specific specialty laboratories for each given assay. We are also exploring the best means for using banked samples from matched, untreated people with ALS for biomarker comparisons.
Clinical efficacy assessments are performed at baseline and at the end of each treatment cycle. Adverse events related to the study are collected.
Results: A total of 33 patients have been enrolled as of June 2021. Biosamples from the baseline visit and the first cycle of treatment from the first 16 participants were analyzed for all assays as a pilot evaluation of study and assay processes. Large fractions of the 3-nitrotyrosine and 4-hydroxynenal results were below the limit of detection, and these assays are being revised. All other assays provided reliable results. Greater than 7000 somamers from the SomaLogic platform passed quality control. Analysis pipelines were developed for data transfer and analysis to address within-cycle pharmacodynamic response and association with clinical outcomes.
Discussion: The results of this study may help to identify biomarkers predictive of response to edaravone and biomarkers of pharmacodynamic response to edaravone that may elucidate biological mechanisms. The results will further evaluate the safety and efficacy of edaravone in treating patients with ALS in a real-world setting.

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CLT-30 A phase 2 safety and tolerability study of an anti CD40LG antibody, AT-1501 in adults with ALS

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Background: Amyotrophic lateral sclerosis (ALS) is a fatal, degenerative disorder characterized by progressive wasting and paralysis of voluntary muscles. Neuroinflammation is a key mediator of ALS disease progression. Reactive astrocytes and microglia as well as infiltrating lymphocytes, dendritic cells, monocytes and macrophages have been characterized in animal models of ALS and at autopsy in patients. CD40LG and the costimulatory pathway, which modulates signaling between antigen presenting cells and activated T cells, was identified in the spinal cord, sciatic nerve, and skeletal muscle in rodent models of ALS. The observations of costimulatory

pathway activation seen in the murine ALS model were then confirmed in humans. Blocking CD40LG in a rodent model of ALS reduces macrophage attack on peripheral nerves, improves neuromuscular junction occupancy, reduces neuroinflammation, slows progression, and improves survival (1). CD40LG is a costimulatory type II membrane receptor for CD40. The binding of CD40LG on T helper cells to CD40 on antigen presenting cells induces multiple downstream immune and inflammatory responses, including B and T cell clonal expansion, antibody production and the production of pro-inflammatory cytokines and chemokines. AT-1501 is a humanized IgG1 antibody that blocks CD40LG signaling. AT-1501 has high affinity binding to human CD40LG and lacks Fc effector function eliminating risk of platelet activation and thromboembolisms. In a phase 1, single ascending dose study in healthy volunteers and adults with ALS, AT-1501 (0.5, 1, 2, 4 and 8 mg/kg) demonstrated a favorable safety signal, linear pharmacokinetics across all dose ranges, minimal anti-drug antibody responses and functional activity against a KLH challenge. These data support the further development of AT-1501 in adults with ALS.
Methods: This is a phase 2a, multi-center, open label, dose escalation study of AT-1501. Approximately 54 adults with ALS will be enrolled in up to 13 clinical sites in North America. Four ascending doses of AT-1501 (1.0, 2.0, 4.0 and 8.0 mg/kg) will be administered as a 1-h IV infusion to sequentially enrolling cohorts. The 1.0 and 2.0 mg/kg cohorts will consist of 9 participants each and the 4.0 and 8.0 mg/kg cohorts will consist of 18 participants each. The participants in each cohort will receive 6 bi-weekly infusions of AT-1501. The primary objective is to assess the safety and tolerability of AT-1501 in adults with ALS. Exploratory endpoints include changes in ALSFRS-R and respiratory function from baseline, evaluation of biomarkers of target engagement, and changes in pro-inflammatory cytokines and neurofilament light chain in circulation from baseline.

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Reference

1. Lincecum, J, Vieira, F, Wang, M, et al. Nat Genet. 2010;42(5): 392–9.

CLT-31 Lived experience of persons with amyotrophic lateral sclerosis who are participating in a clinical trial (work in progress)

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Background: Currently only Riluzole and edaravone are approved for the treatment of ALS (amyotrophic lateral sclerosis) (1). With only two therapies approved for a devastating disease, clinical trials are crucial for the development of new drugs. Patient participation in clinical trials is vital to progress the development of potential therapies. Studies have looked at the barriers and facilitators to recruitment, both from the patient and physician perspective (2); however there remains a lack of knowledge on the lived experience during a Person with ALS's (PwALS) participation in a clinical trial. As the physical effects of ALS can already take a grand toll on a patient's daily functioning, it is essential to understand the factors that encourage a patient to participate in a research study.
Objectives: To study PwALS's lived experience during their participation in a clinical trial.
Methods: This will be a qualitative study. Study participants with the defined criteria will be interviewed once. Approximately 15–20 participants will be recruited. Those who are currently participating in a clinical trial for ALS will be eligible to participate. A semi-structured interview will be conducted with each participant.
Results: This is a work in progress. Interviews will be transcribed. Common themes will be formulated and presented in a visual diagram.
Conclusions: This is a work in progress. Themes extracted from the data analysis will provide greater insight into a PwALS's lived experience during a clinical trial, and in particular, what keeps them motivated to stay in the trial. With this information, the clinical team can better prepare patients entering a trial, as well as potentially provide more tools for better support.

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References

1. Valko K, Ciesla L. Prog Med Chem. 2019;58:63–117.
2. DasMahapatra P, Raja P, Gilbert J, et al. Clinical trials from the patient perspective: survey in an online patient community. BMC Health Serv Res. 2017;17:166.

CLT-32 Study design for a phase 3, multicenter, open-label, safety extension study of investigational oral edaravone administered over 96 weeks in patients with ALS (MT-1186-A03)

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Background: Radicava® (edaravone injection) is a US Food and Drug Administration–approved treatment for ALS that was shown to slow the rate of physical functional decline (1,2). There is interest in a non-intravenous (non-IV) formulation of edaravone and an ongoing, multicenter phase 3 study (MT-1186-A01) is currently assessing the safety and tolerability of an investigational oral formulation of edaravone (MT-1186).
Objective: To assess the long-term safety and tolerability of investigational oral edaravone in patients with ALS.

Methods: Study MT-1186-A03 is a safety extension study of Study MT-1186-A01, which is an ongoing global, multicenter, open-label phase 3 study evaluating the long-term safety and tolerability of investigational oral edaravone in patients with ALS. Study MT-1186-A01 includes a screening period of ≥3 weeks, an open-label treatment period of 48 weeks, and a safety follow-up period of 2 weeks after the last dose. Entry criteria include males and females aged ≥18 years to 75 years, with an ALS diagnosis of definite ALS, probable ALS, probable laboratory-supported ALS, or possible ALS, according to El Escorial criteria; baseline forced vital capacity ≥70% predicted; disease duration ≤3 years; and functioning independently.
Patients are receiving a 105-mg dose of investigational oral edaravone administered in treatment cycles that replicate the dosing of IV edaravone. This includes an initial treatment cycle with daily oral dosing for 14 days, followed by a 14-day drug-free period. Subsequent treatment cycles consist of daily oral dosing for 10 days of a 14-day period, followed by a 14-day drug-free period. Treatment cycles are every 4 weeks.
In addition to the primary safety analysis, Study MT-1186-A01 also includes exploratory end points, such as change from baseline in the revised ALS Functional Rating Scale (ALSFRS-R) score and time to death, tracheostomy, or permanent assisted mechanical ventilation.
Patients who complete treatment in Study MT-1186-A01 will be eligible to be enrolled in this open-label treatment extension study (MT-1186-A03). It is anticipated that Study MT-1186-A03 will include approximately 140 patients. All patients will receive investigational oral edaravone once daily. Treatment cycles will occur every 28 days (10 days on study drug out of a 14-day period, followed by 14 days off study drug). The primary objective of this extension study is to evaluate the continued long-term safety of investigational oral edaravone, and the study includes exploratory efficacy end points in common with Study MT-1186-A01.
Results: Ongoing.
Discussion: This extension study of investigational oral edaravone will provide important information on the long-term safety and tolerability of this new formulation of edaravone in patients with ALS.

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References

1. RADICAVA® (edaravone injection) [package insert]. Jersey City, NJ: Mitsubishi Tanabe Pharma America, Inc; 2021.
2. Writing Group; Edaravone (MCI-186) ALS 19 Study Group. Lancet Neurol. 2017;16(7):505–12.

CLT-33 ALS clinical trial engagement: perspectives from patients and healthcare staff at one institution in the Midwest (United States)

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Introduction: Scant evidence exists as to patient preferences regarding amyotrophic lateral sclerosis (ALS) clinical trials with little documentation why patients do not enroll in trials. The purpose of this study is to understand why ALS patients do or do not choose to participate in clinical trials. Engaging with patients and healthcare staff directly is important to gather the perspectives of our ALS community and identify barriers to trial enrollment.
Methods: Between 2020 and 2021, nine individuals associated with ALS at the University of Iowa Hospitals and Clinics were interviewed. The qualitative team conducted semi-structured interviews with patients ($n = 2$), healthcare staff ($n = 6$), and an advocacy group representative ($n = 1$), asking open-ended questions to explore their opinions of clinical trials and potential barriers and facilitators to participation. Transcripts of the interviews were coded to determine themes. The team then identified specific subthemes and examples corresponding with each theme.
Results: Four main themes emerged during the interviews: barriers, facilitators, recommendations, and life with ALS. Participants identified distance to clinic as the greatest barrier to trial enrollment. Fatigue from extensive travel and long study visits contributed to lack of interest or early withdrawal from trials. Virtual study visits were considered a positive potential attribute to clinical trials. However, interviewees expressed frustration with their telemedicine experiences including lack of technology savviness and disrupted video connections. Participants agreed hope for a cure is the main facilitator of clinical trial participation. Although many patients did not believe the trial would help their prognosis, they hoped their participation would benefit future patients. Patient awareness of clinical trials was cited as beneficial for enrollment. Patients rely on clinic staff, and sometimes social media, to educate them about trials. The most common recommendation to improve clinical trial participation revolved around education and marketing. Patients may be more likely to enroll in trials if they thoroughly understand the trials' protocols. Sharing stories of past participants can help normalize trials. Interviewees expressed ways to improve study visits to make them more attractive to patients such as combining clinical trial visits with standard of care clinic visits. Lastly, participants identified a need for more research on technology, assistive devices, and ALS services commenting that non-pharmaceutical research can improve quality of life.
Conclusions: This qualitative study identifies potential areas of focus for improving clinical trial engagement for patients with ALS. Themes emerged from interviews with ALS patients and healthcare staff emphasizing trial accessibility, patient awareness and understanding of clinical trials, and shared goals of the trials being offered. Future directions include

continuation of interviews and utilizing the identified themes in a survey distributed to all ALS patients followed at the University of Iowa.

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CLT-34 A composite endpoint for ALS clinical trials based on patient preference: Patient-Ranked Order of Function (PROOF)

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Rationale: Patients with amyotrophic lateral sclerosis (ALS) are affected in multiple domains, limiting their bulbar, arm, leg and/or respiratory function. Classically, these domains are summarized into total scores, which serve as primary endpoints in clinical trials. The importance of each domain, however, may vary between patients and is not accounted for in a total score. Current clinical trial endpoints, therefore, may not reflect what is most important for the patient and could over- or undervalue new treatments.
Objective: Here we propose a new composite endpoint for randomized controlled clinical trials in ALS based on the patient preference for functional domains.
Methods: An online questionnaire was sent out to a population-based registry in the Netherlands. Patients with ALS were asked to score functional domains with a validated self-reported questionnaire, and rank the order of importance of each domain. The questionnaire information was used to estimate variability in patient preferences and to develop the Patient-Ranked Order of Function (PROOF) test statistic for clinical trials.
Results: In total, 500 out of the 668 patients (74.9%) responded, of which 433 completed the questionnaire. The majority of the patients (64.6%) indicated to prefer prioritizing certain domains over others when evaluating treatments. The PROOF endpoint was defined such that each patient is compared to all other patients based on their preferred order of functional domains. In each comparison, a patient can be scored as winner, loser or equal to its comparator. PROOF averages all pairwise comparisons for the experimental arm and reflects the probability that a random patient receiving treatment has a more desirable outcome than a random patient receiving placebo. By means of simulation we illustrate how incorporating patient preference may up- or downgrade trial results compared to classical endpoints, and could potentially result in significant efficiency gains.
Conclusion: As patients differ in their disease experience and personal needs, accounting for patient preferences in efficacy endpoints can be an important step towards more patient-centric clinical trials and to appropriately value new treatments.

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CLT-35 Overview of the Healey Center's Expanded Access Protocol Programs for investigational treatments in amyotrophic lateral sclerosis

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Background: Expanded access protocols (EAPs) occupy a space between formal clinical research trials and routine clinical care. They provide patient access to experimental treatments in clinical development to people who are not eligible for clinical trials. People with advanced ALS are often excluded from clinical trials, which focus on evaluating the impact on early disease trajectory. EAPs can provide useful data on safety and treatment-related biomarkers that can be utilized for drug development.
Methods: The maintenance of a successful EAP program requires the study team to safely provide the treatment under FDA and IRB oversight. The Healey Center for ALS at Massachusetts General Hospital currently manages nine expanded access protocols, including three single-patient and six intermediate-sized protocols, with nine different investigational therapies. For larger expanded access protocols, investigators utilize standardized patient-centric electronic data capture (EDC) platform, NeuroREACH™.
Results: From July 2018 to May 2021, 130 people with ALS have enrolled across all of the Healey Center's EAPs. 93 of these participants were male and 37 were female. Average time from symptom onset to screening was 59 months. Site of ALS symptom onset was limb for 91 patients, bulbar for 30 patients, and a different site for 6 patients. In response to the coronavirus 2019 pandemic (COVID-19), our center made updates to our programs. In addition to initiating remote consenting for all EAPs, nearly all study visits are now completed remotely. Study staff completes follow up with participants via telephone or virtual call, and the participants complete other outcomes at a local lab or physician's office. In the case of necessary study drug dispensation, study staff ships the medication to participants, and used medication containers are shipped back to the site for purposes of drug accountability.
Conclusions: While COVID-19 has introduced numerous challenges to our site, our response has allowed us to continue providing access to medications and to monitor for safety in a way that protects both patients and study staff from risk. Sharing our experience may help other academic centers to establish EAPs. Furthermore, innovations in virtual visit follow-up and approaches to ease participant burden in our EAP programs may prove to be helpful for trials in ALS and other neurological disorders.

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CLT-36 Grip strength is more than a number: the relationship between grip strength and fine motor and arm function in FORTITUDE-ALS

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Background: FORTITUDE-ALS (NCT03160898) was a 12-week, Phase 2, double-blind trial of reldesemtiv in 458 patients with ALS randomized to 1 of 3 reldesemtiv doses or placebo. Outcome measures included ALS Functional Rating Scale-Revised (ALSFRS-R), grip strength (GS), and ALSAQ-5. While GS is frequently performed as an outcome measure in ALS clinical trials and may be part of routine ALS care, the relationship of declining GS and the impact on fine motor function or on health-related quality of life for arm function has not been previously described.
Objectives: To investigate the relationship between GS and fine motor function as measured by the fine motor domain sub-score (FMDS) of the ALSFRS-R and GS and the patient's perception of difficulty using their arms and hands as measured by responses to Question 2 of the ALSAQ-5 (higher values reflect worse function). Fine motor domain questions include handwriting (HW), cutting food (CF) and dressing/hygiene (DH).
Methods: ALSFRS-R, bilateral GS and the ALSAQ-5 were collected at Screening, Day 1, Weeks 2, 4, 8, 12 and follow-up. The average GS combined for both hands (GSbh) were summarized by ranges of the FMDS and the decline in FMDS for male, female and both sexes combined using descriptive statistics. The strength of correlations between GSbh and FMDS and between GSbh and Question 2 of the ALSAQ-5 were evaluated using Spearman's correlation.
Results: The Spearman correlation coefficient for the FMDS and GSbh was 0.723 ($p < 0.0001$). The Spearman correlation coefficient for Question 2 of the ALSAQ-5 and GSbh was –0.634 ($p < 0.0001$). Patients with a FMDS of 0–2 had a mean GSbh of 4.97 ± 7.02 lbs, FMDS of 3–5 had mean GSbh of 14.9 ± 11.4 lbs, FMDS of 6–8 had mean GSbh 31.9 ± 17.5 lbs and FMDS of 9–12 had a mean GSbh 53.2 ± 23.1 lbs for both sexes combined. Similar patterns were seen for females and males, with higher values seen for men. The mean GSbh score was numerically lower with each drop of one point on the individual items of the fine motor domain; this was true for males, females, and both sexes combined. For the 44 patients whose baseline FMDS was 12, DH scores declined before CF or HW scores. When comparing the GSbh for items scored 3, 2, or 1, in general higher GSbh results were found for DH > CF > HW.
Discussion: GSbh showed a strong correlation with the FMDS and a moderate correlation with patient perceived difficulty using their arms. These findings offer support that the GSbh has clinical and patient relevance as an outcome measure in ALS clinical trials.

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CLT-37 Safety and efficacy of dimethyl fumarate in ALS: randomized controlled study

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Objective: Neuroinflammation is an important pathogenic mechanism in amyotrophic lateral sclerosis (ALS), with regulatory T cells (Tregs) mediating a slower rate of disease progression. Dimethyl fumarate enhances Treg levels and supresses pro-inflammatory T cells. The present study assessed safety and efficacy of dimethyl fumarate in ALS.
Methods: Phase-2, double-blind, placebo-controlled randomized clinical trial recruited participants from 1 May 2018 and 25 September 2019, across 6 Australian sites. Participants were randomized (2:1 ratio) to dimethyl fumarate (480mg/d) or matching placebo, completing visits at screening, baseline, weeks 12, 24 and 36. The primary efficacy endpoint was change in Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R) at week 36. Secondary outcome measures included survival, neurophysiological index (NI), respiratory function, urinary neurotrophin-receptor p75, and quality of life.
Results: A total of 107 participants were randomised to dimethyl fumarate ($n = 72$) or placebo ($n = 35$). ALSFRS-R score was not significantly different at week 36 (−1.12 (−3.75 to 1.52, $p = 0.41$). Dimethyl fumarate was associated with a reduced NI decline week 36 (differences in least squares mean: (0.84 [−0.51–2.22, $p = 0.22$). There were no significant differences in other secondary outcome measures. Safety profiles were comparable between groups.
Conclusion: Dimethyl fumarate, in combination with riluzole, was safe and well tolerated in ALS. There was no significant improvement in the primary endpoint. The trial provides class I evidence for safety and lack of efficacy of dimethyl fumarate in ALS.

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CLT-38 Enabling effective public involvement: a case study of involvement in the HighCALS research programme

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Programme grants are large, complex pieces of research involving small teams working on different, linked projects, as part of the development of an intervention. Such research lends itself well to public involvement, with discrete, tangible elements providing an opportunity for considered and focused input. However, ensuring effective public involvement within such a broad and varied environment can be challenging, and requires appropriate planning.

The HighCALS programme has focused on the development of an intervention to support people with Motor Neurone Disease (MND) and their carers with nutritional management. The grant has a designated public involvement lead who is in regular contact with a carer co-applicant around progress and to seek appropriate input as the research has progressed.

The grant also provides regular updates to, and seeks input from, a local MND patient and carer research group, the Sheffield Motor Neurone Disease Research Advisory Group. Their input contributed to the development of participant information materials for the early phase work and trial.

Aside from this, the research team has established its own Public Involvement Network within the grant, aiming to extend the opportunity for involvement much wider than the local area, using promotion via social media and Motor Neurone Disease Association networks. People with MND may struggle to attend face-to-face meetings because of mobility or communication difficulties, for example. As such, the Network is focused on providing a flexible approach that allows input via other means, such as email and videoconferencing. This is particularly important in the current climate around COVID-19.

The Network has had an integral role in the development of our intervention, OptiCALS, providing input into its content and format. As we now move into the trial phase of the programme, testing the intervention, regular progress updates will be provided to the Network aside from requests for input, so that people continue to feel engaged with its work. Newsletters will be used as one way of providing such updates, and will look to include member stories – it is hoped that this will help to develop an inclusive community, particularly for those unable to meet face-to-face.

We have worked to be as inclusive as possible, providing opportunities for people with MND and carers, considering their particular needs to facilitate engagement from a wider group of individuals.

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CLT-39 An exploration of the minimally important difference in ALSFRS-R score for patients

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Background: Despite being the most commonly used outcome measure in clinical trials, there is no consensus as to what represents a meaningful change in ALSFRS-R (1) score for patients.

Objectives: We sought to estimate the minimal important difference (MID) for the ALSFRS-R in a prospective cohort of people with ALS. The MID will represent the smallest difference in ALSFRS-R score that is meaningful to patients in terms of a perceptible change in their condition.

Methods: Anchor and distribution based methods were used to estimate the MID scores for patients with ALS in a longitudinal, observational study. ALSFRS-R data were collected at approximately 3 month intervals. Participants answered a global rating of change question (GRoC) to rate how their overall health-related quality of life compared to that at the previous visit. The data were grouped according to GRoC outcome at any given visit ("about the same", "better" or "worse"), with the change in ALSFRS-R scores between that and the previous visit then compared.

Results: A total of 131 people with ALSFRS-R data for both visits 1 and 2 and GRoC data from visit 2 are included in these analyses. According to the GRoC at visit 2, 63 participants reported their overall health as "about the same"; 2 as "better" and 66 as "worse". The monthly rates of change on the ALSFRS-R for each group between visits 1 and 2 were: "worse", −1.24 (SD 1.55), "about the same", −0.43 (SD 1.05), "better", +0.44 (SD 0.28). For the individual domains, the rates of change were: bulbar: "worse", −0.22 (SD 0.58), "about the same", −0.14 (SD 0.38), "better", +0.48 (SD 0.68), motor fine: "worse", −0.37 (SD 0.59), "about the same", −0.10 (SD 0.43) , "better", +0.12 (SD 0.17), motor gross: "worse", −0.36 (SD 0.55), "about the same", −0.16 (SD 0.41) , "better", −0.16 (SD 0.23), respiratory: "worse", −0.29 (SD 0.91), "about the same", −0.03 (SD 0.42) , "better", 0.00 (SD 0.00).

Discussion: Analyses indicate that the MID for the ALSFRS-R is approx 1.2 points per month. The results of this study can assist clinicians and researchers in the interpretation of

ALSFRS-R scores for comparisons between groups or within groups of people with ALS.

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Reference

1. Cedarbaum J, Stambler N, Malta E, et al. J Neurol Sci. 1999; 169(1–2):13–21.

CLT-40 Development and evaluation of a patient reported outcome in amyotrophic lateral sclerosis (PRO-ALS)

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Background: Currently, the ALSFRS-R is the most commonly used questionnaire to measure disease progression and is a recommended efficacy outcome for ALS clinical trials. The ALSFRS-R, however, presents a series of limitations, which affects its utility as a clinical trial endpoint.
Objectives: (1) develop a patient-reported and remote questionnaire that measures disease progression in ALS, (2) evaluate the questionnaire as a trial endpoint by comparing the required sample size with the ALSFRS-R.
Methods: A preliminary ALS questionnaire with 110 questions was developed based on literature review, clinical judgement of an expert panel and input from ALS patients. ALS patients enrolled in the Netherlands Neuromuscular Biobank were sent an invitation per e-mail to participate in this online study. Questionnaire answers were recorded in an online database. Reliability per item was determined by a 2 week test-retest and items with an ICC less than 0.80 were removed from the preliminary questionnaire. In the longitudinal phase, patients completed the digital questionnaire every 2 months remotely for 12 months. Rasch analyses were performed and items that showed disordered thresholds or item bias were systematically removed. Longitudinal decline per item was evaluated using linear mixed effects models. The final questions per bulbar, motor and respiratory subscale were selected by comparing rate of decline, between-patient variability and required sample size. Sample size calculations were based on 80% power to detect a 35% reduction in rate of decline in a 12-month clinical trial. Sample size reductions relative to the ALSFRS-R subscales were calculated.
Results: The preliminary questionnaire and the ALSFRS-R were sent to 747 patients, and 479 (64.1%) provided informed consent and completed at least one questionnaire. In total, 2821 questionnaires were completed during 12 months follow-up with a mean of 5.9 questionnaires and 9.5 months of follow-up time per patient. Out of 110 questions, 66 (60%) questions had an ICC of 0.80 or higher, reflecting high test-retest reliability. Unidimensional bulbar (4 items), motor (6 items) and respiratory (4 items) subscales were constructed with each item scored 0, 1 or 2. Compared with the ALSFRS-R, endpoint variability per subscale was lower and average rate of decline higher. Consequently, required sample size for a 12-month clinical trial was reduced by 22.2%, 13.8% and 64.4% for bulbar, motor and respiratory subscales, respectively.
Discussion: The self-reported PRO-ALS questionnaire had high test-retest reliability, improved item targeting and lower endpoint variability compared to the ALSFRS-R. As a result, PRO-ALS requires smaller sample sizes to detect a given treatment effect or is able to detect smaller treatments effects with equal sample sizes. Using optimal endpoints is important to accelerate identification of effective treatments for ALS.

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CLT-41 RNS60 and ALS: biological and clinical effects

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Background: RNS60 is a novel, anti-inflammatory and cyto-protective drug that has shown remarkable efficacy in animal models of neuroinflammation and neurodegeneration. In a pilot open-label trial, the feasibility, safety, and tolerability of long-term RNS60 administration was demonstrated in people with ALS.
Methods: These findings prompted us to organize a multi-center, randomized, double-blind, placebo-controlled, parallel group, add-on trial on the use of RNS60 in ALS patients that has been recently completed. Patients were randomized to receive RNS60 (active) or placebo while concomitantly taking riluzole (50-mg twice a day). RNS60 or placebo was administered intravenously once a week and inhaled via nebulization every morning in the remaining week-days for 24 weeks. Each patient was monitored for 48 weeks (24-week treatment +24-week follow up) or until death, whichever occurred first. Blood samples for biomarker analysis (at RNA and proteins level) were collected on day 1 and at week 4, 12, 24, and 48. Safety and efficacy were assessed by way of physical examination, vital signs and AEs. Changes in disability and quality of life were assessed using the ALSFRS-R scale, Forced Vital Capacity (FVC) and ALSAQ-40 scale.
Objectives: Primary Objective: to measure the effect of RNS60 treatment on selected pharmacodynamic biomarkers in peripheral blood of ALS patients concurrently treated with riluzole. Candidate markers were: MCP-1, cyclophilin A, nitrated actin, 3-nitrotyrosine, IL-17, NfL and Tregs (measured via FOXP3 and CD25 mRNA). *Secondary Objectives*: the effect on functional impairment, as measured by the ALSFRS-R scale; the effect on respiratory function as measured by forced vital capacity (FVC); the impact on quality of life as measured by ALSAQ-40 scale (5 domains: physical mobility, ADL and independence, eating and drinking, communication,

emotional reactions); the effect on self-sufficiency defined as a score of 3 or higher on all the 3 domains walking, cutting food and handling utensils, swallowing of ALSFRS-R scale; the effect on survival (defined as being alive without tracheostomy); the tolerability and safety of RNS60 through the identification of unexpected adverse events.
Results: 147 patients were enrolled, 99 women and 48 men, aged 30–77 years, with definite, probable or probable laboratory supported ALS and mild to moderate functional impairment at admission. Spinal onset ALS was documented in 85.7% of cases.
Discussion: Statistical analyses are ongoing and final study results will be presented.

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CLT-42 Using a patient-based registry as a pre-screening tool for ALS trials: the role of vital capacity

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Background: The Swedish Motor Neuron Disease (MND) Quality Registry (MND-reg) collects more than 100 variables per patient diagnosed with different MNDs including amyotrophic lateral sclerosis (ALS), striving for evaluable and equivalent care and treatment for ALS patients in Sweden (1).
Currently in Sweden, out of 30 sites keeping MND-reg, only two regularly conduct ALS trials, stressing the need to develop a standardized pre-screening protocol by considering the entire Swedish ALS/MND population for clinical trials, using the national MND-reg as the tool.
Four criteria are considered the most important when pre-screening patients for ALS trials, forced vital capacity (FVC) being one of the most determinant. Latest data collection of the MND-reg shows however that the registry is not regularly updated with FVC values, excluding patients who should have been considered for participation in trials.
Objectives: Establish the Swedish MND-reg as a pre-screening tool for ALS trials in Sweden.
Methods: 220 existing ALS patients from the Stockholm-region registered in the MND-reg had their profile updated with FVC values. We conducted a medical journal review of all patients, including both the neurological and respiratory care. The number of patients considered for pre-screening was compared before and after updating the registry with the missing FVC values from the medical charts.
Results: 189 out of the 220 ALS patients registered in the Stockholm-region had no FVC values registered in the MND-reg, implying that only 31 could have been considered for trial eligibility. Through the medical record review, 205 values were entered into the system, updating the profiles of 114 ALS patients.
FVC values above 60% were entered for 74 of the 114 patients. Among these 74 patients, only 20 had previous registrations of their FVC values above 60%. Indicating that, considering the 60% limit for ALS inclusion, 270% more patients were eligible, going from 20 to 74 patients.
Conclusion: The MND-reg is a powerful tool that could be used along in pre-screening for clinical trials. However 86% of the registered ALS-patients could not be considered for eligibility in a pre-screening process, not due to exclusion criteria, but because the variable FVC values had not been entered into the registry even when indeed measured. Considering that 95% of ALS patients with complete information on inclusion and exclusion criteria will eventually be excluded from trials (2), collecting crucial data on criterium variables in MND-reg and any other ALS quality registers is fundamental to make trials available to more patients with ALS.

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References

1. Longinetti E, Regodón Wallin A, Samuelsson K, et al. The Swedish motor neuron disease quality registry. Amyotroph Lateral Scler Frontotemporal Degener. 2018;19(7–8):528–37. doi: 10.1080/21678421.2018.1497065.
2. van Eijk RPA, Westeneng HJ, Nikolakopoulos S, et al. Refining eligibility criteria for amyotrophic lateral sclerosis clinical trials. Neurology. 2019;92(5):e451–60. doi: 10.1212/WNL.0000000000006855.