CLT-02: A double-blind, placebo-controlled, clinical trial after curcumin supplementation in Amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is a multifactorial disease in which genetic and environmental factors contribute to its pathogenesis for which oxidative stress is considered to play a key role. Curcumin, a natural compound, in know for its neuroprotective and antioxidant capacities, suggesting that it could improve pathological conditions involving redox equilibrium alterations, such as ALS. After the encouraging results of our previous trial using Brainoil (600 mg/day) in ALS patients, the current study has been designed to determine whether high dose curcumin oral supplementation (1500 mg/day, Alibrain Advanced, produced by Aliveda Laboratories, Pisa, Italy) may be further efficacious in the tretment of disease. ALS patients were randomized to receive, for 6 months, a treatment with curcumin (Curcumin Group, CG, n11) or placebo (Placebo Group, PG, n=9). Both clinical and anthropometric parameters, such as ALS-functional rating scale (ALS-FRS), medical research council (MRC), weigth, body mass index (BMI), as well as blood levels of oxidative stress biomarkers, including oxidative protein products (AOPP), ferric reducing ability (FRAP), total thiols (t-SH), were evaluated before (T0), after 3 months (T1), and after 6 months (T2) of curcumin or placebo treatment.Comparison considering inter-group (CG vs PG), single evaluation times, and intra-group (CG or PG), between times (T2-T1-T0) evaluations were carried out. Over the entire study no change was observed in the clinical and anthropometric parameters after curcumin administration. The intra-group analysis showed that AOPP levels in PG significantly increased at T1>T0 ($p=0.01$), while in CG they remained unchanged over time ((T2-T1-T0, p=ns). In CG, with respect to PG, FRAP increased after curcumin administration both at T1>T0 ($p\leq0.001$) and at T2>T1 ($p\leq0.01$), as did t-SH at T1>T0 ($p=0.02$), with a positive trend also after 6 months of curcumin administration (T2-T0, $p=0.06$). The inter-group analysis revealed in CG compared to PG lower AOPP levels, at T1 ($p=0.02$) and T2 (not significant, $p=0.07$), as well as significant higher FRAP and t-SH levels at T1 and T2 ($0.01\leq p\leq0.001$). Treatment with curcumin in ALS confirms encouraging results as modulator of th intracellualr redox homeostasis, decreasing the oxidative damage, as observed by the rise of FRAP and t-SH levels. Although the clinical course of the disease did not change over the 6 months considered duration of the study, results suggest that further studies are worthy to be done in order to confirm these data, at the same time contributing to deepen knowledge into pathogenic mechanisms of ALS.

CLT-03: A Machine-Learning ALS Survival Model Lacking Vital Capacity for use in Clinical Trials during the COVID-19 Pandemic

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Introduction:
The ongoing COVID-19 pandemic has made it difficult in some clinical settings to measure vital capacity for the purpose of eligibility determination. We developed a machine learning survival model without the use of baseline vital capacity measures and asked whether it could stratify clinical trial patients and a wider ALS patient population derived from a tertiary care ALS center (Emory University).

Methods:
A ML gradient boosting machine survival model (noVCSurv) lacking baseline vital capacity measures was trained using the PRO-ACT database and compared to a previously validated survival model that included vital capacity (VCSurv). Kaplan-Meier survival curves using strata generated by the noVCSurv model were compared to strata created using baseline vital capacity cut-offs for a clinical trial data set and a clinic data set.

Results:
The noVCSurv model suffered a minor decline in performance compared to the VCSurv model. When analyzed using clinical trial data, the noVCSurv model replicated the strata created using baseline vital capacity. When analyzed using the Emory Clinic data, the noVCSurv model outperformed strata created using baseline vital capacity.

Conclusions:
The noVCSurv model offers an alternative to the use of vital capacity for eligibility determinations during the COVID-19 pandemic. The observation that the noVCSurv model outperforms the use of vital capacity for eligibility determinations in a broad ALS patient population suggests the use of strata generated using prognostic models as future ALS clinical trial eligibility criteria.

CLT-04: A Phase 3, Multi-Center, Double-Blind, Randomized, Placebo Controlled Trial to Evaluate the Efficacy and Safety of Reldesemtiv in Patients with Amyotrophic Lateral Sclerosis (ALS): COURAGE-ALS Trial Design

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Background:
FORTITUDE-ALS (NCT03160898) was a 12-week, phase 2, double-blind study of reldesemtiv in 458 patients with ALS randomized to 1 of 3 reldesemtiv doses or placebo. Outcome measures included slow vital capacity (SVC), ALS Functional Rating Scale-Revised (ALSFRS-R), and quantitative muscle strength. Although the primary analysis of the change in SVC from baseline to Week 12 did not reach statistical significance, positive trends were noted in SVC, ALSFRS-R, and muscle strength. The effect was more evident in patients with shorter symptom duration and faster progression rates. There was a dose dependent decrease in eGFR on reldesemtiv that reversed with discontinuation.

Objective:
To design a phase 3 trial studying the impact of reldesemtiv at a dose of 300 mg BID on patients with ALS, building on insights gained from FORTITUDE-ALS with respect to dose level, the appropriate patient population, and adverse events.

Methods:
COURAGE-ALS (Clinical Outcomes Using Reldesemtiv on ALSFRS-R in a Global Evaluation in ALS) will be a double-blind, phase 3 study in which approximately 555 patients with ALS will be randomized to 24 weeks of reldesemtiv 300 mg PO BID or matching placebo with a 2:1 active to placebo ratio, followed by a 24-week period in which all patients will receive reldesemtiv 300 mg PO BID. Eligible patients will be within 2 years of first symptom of weakness, have vital capacity of ≥ 65% predicted, and a screening ALSFRS-R ≤ 44. Stable doses of edaravone and/or riluzole will be permitted and patients will be stratified accordingly. The primary outcome measure will be change from baseline to 24 weeks in ALSFRS-R. Secondary endpoints will 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 for vital capacity; ALSAQ-40; and bilateral handgrip strength. Selected exploratory endpoints will include time to receipt, first and substantial use of durable medical equipment; time spent in each MiToS (Milano Torino Staging) stage and number of stages moved; and hand-held dynamometry (HHD) of selected intrinsic hand muscles. Two unblinded interim analyses by the DMC are planned; the first will occur 12 weeks after approximately one-third or more of the planned sample size is randomized and is for futility only. A second interim analysis will also look at futility but there will be an option of a fixed increase in total enrollment if necessary to augment the statistical power of the trial.

Conclusion:
COURAGE-ALS will be a phase 3 trial designed to evaluate the hypothesis that fast skeletal muscle activation using reldesemtiv constitutes an important therapeutic strategy in ALS.

CLT-05: A systematic review of neuropsychiatric and cognitive assessments used in clinical trials for amyotrophic lateral sclerosis.

Miss Emily Beswick[1], Miss Emily Park[3], Dr Charis Wong[2], Dr Arpan Mehta[6], Dr Rachel Dakin[2], Professor Siddharthan Chandran[6], Mrs Judith Newton[2], Professor Alan Carson[1], Professor Sharon Abrahams[5], Dr Suvankar Pal[1]

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Background:
Up to 50% of people with amyotrophic lateral sclerosis (ALS) experience cognitive dysfunction [1]. A recent population based study in Scotland reported a prevalence of neuropsychiatric disorders of 19.7% in people with ALS, 70% of which were mood disorders and 31.67% neurotic disorders (inclusive of anxiety, stress-related and somatoform disorders) [2]. These symptoms impact on quality of life, and are associated with poorer prognosis. Historically, outcomes in clinical trials have focused on the effect of candidate drugs on physical functioning.

Methods:
We reviewed the last 25 years of clinical trials of investigative medicinal products in people with ALS, since the licensing of riluzole, and extracted data on frequency and type of assessment for neuropsychiatric symptoms and cognitive impairment. Trial registry databases including WHO International Trials Registry, European Clinical Trials Register, clinicaltrials.gov, and PubMed were systematically searched for Phase II, III or IV trials registered, completed or published between 01/01/1994 and 31/10/2019. No language restrictions were applied. Outcome measures, exclusion criteria and assessment tool used were extracted.

Results:
216 trials, investigating 26,326 people with ALS were reviewed. 35% assessed neuropsychiatric symptoms, and 22% assessed cognition, as Exclusion Criteria or Outcome Measures. 3% (n = 6) of trials assessed neuropsychiatric symptoms as a Secondary Outcome Measure, and 4% (n = 8) assessed cognition as Outcome Measures; only one trial included assessments for both cognition and neuropsychiatric symptoms as Outcome Measures. Three ALS-specific assessments were used in six trials.

Conclusions:
Trials for people with ALS have neglected the importance of neuropsychiatric symptoms and cognitive impairment. Evaluation of these extra-motor features is essential to understand the impact of candidate drugs on all symptoms of ALS.

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CLT-06: Assessing inter-rater reproducibility of a novel MUNE method MScanFit MUNE in a single subject Round Robin setup.

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Objective:
Consensus on a reliable Motor Unit Number Estimation (MUNE) method for diagnosing and monitoring neurodegenerative diseases where collateral muscle reinnervation takes place has not been achieved. In 2017 the novel MUNE-method MScanFit MUNE was demonstrated to be sensitive and specific when comparing healthy controls and ALS-patients, making it a possible biomarker for ALS. The aim of our study was to assess the inter-rater reliability of MScanFit using a "Round-Robin" research design.

Methods:
Twelve raters examined 6 healthy subjects over the course of two days. Stimulation was performed on the median, ulnar and common peroneal nerves and CMAP-scans were recorded from abductor pollicis brevis (APB), abductor digiti minimi (ADM) and anterior tibial (TA) muscles respectively. Subjects scored their overall perception of pain from the examinations on a numerical rating scale from 0 (no pain) to 10 (unbearable pain).

Results:
Coefficient of variation were (COV): 13.4 for APB, 6.3 for ADM and 5.6 for TA. Limits of agreement (LOA) on the MUNE-values were: 19.5 for APB, 29.8 for ADM and 20.7 for TA compared to mean MUNE-values: 99.6 for APB, 131.4 for ADM and 126.2 for TA. MScanFit association with CMAP peak amplitude was, R^2: APB=0.463, ADM=0.421, TA=0.645. 41.6% of the raters had performed MScanFit ≤5 times prior to these examinations. The subjects scored their average perception of pain as 4 out of 10.

Conclusion:
MScanFit is indicated to have a high level of inter-rater reliability despite a low grade of rater experience. The technique was indicated to be strongly associated with the peak CMAP amplitude, and furthermore only moderately uncomfortable and certainly endurable.

CLT-07: Cannabinoids for symptom management in ALS: exploring approaches to a clinical study

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ALS is associated with a number of debilitating symptoms that can severely affect quality of life (QoL), including pain, muscle cramps, spasticity, loss of appetite, sialorrhea, anxiety, depression and insomnia. These are all symptoms for which cannabis-based medicines have previously shown efficacy. Thus, cannabis-based medicines have great potential for symptom management in people with ALS (PALS).

Δ9-tetrahydrocannabinol (THC) is the best understood component of cannabis and is responsible for its psychoactive effects. It has also been shown to reduce inflammation, relieve pain, stimulate appetite, reduce spasticity, and improve sleep, among other benefits. Cannabidiol (CBD) is the major non-psychotropic component of cannabis and has similarly been studied for its beneficial properties, including its anti-inflammatory, anti-anxiety, and antiemetic actions.

Further to investigating the potential of cannabis in managing targeted symptoms in PALS, a number of studies have implicated the endocannabinoid system in the pathogenesis of ALS and have suggested that cannabinoids may have a disease-modifying effect. For example, in the hSOD1G93A transgenic mouse model of ALS, THC, CBD, cannabinol (CBN), and endocannabinoid receptor agonists have been shown to delay disease progression and prolong survival. Furthermore, given the widely supported role of neuroinflammation in ALS, and the fact that cannabinoids are known to have immune-modulatory effects, it is hypothesized that engagement of endocannabinoid receptors by cannabinoids could have the potential to reduce inflammation and therefore have a neuroprotective effect in PALS. This is supported by evidence of increased expression of endocannabinoid receptors in the spinal cords of PALS, which may suggest an adaptive endogenous neuroprotective mechanism, that could be further exploited through cannabis-based medicines.

Cannabis-based medicines have emerged as a symptom management option for PALS in Canada. The legalization of cannabis in Canada has expanded access to both patients and researchers, and is helping to reduce the stigma around using cannabis. However, there remains a lack of information around dosing, and optimal THC to CBD ratios for symptom management in PALS. Few clinical investigations of cannabis-based medicines have been conducted in PALS, and more evidence is needed on its potential for overall symptom management and QoL improvement, as well as disease modification.

As a first step to addressing this gap, we plan to conduct a study investigating cannabis-based medicines for symptom management in PALS and in preparation, have explored design approaches, accounting for current regulatory considerations. We have identified a number of clinical and patient-reported outcome measures from the cannabis and ALS fields that will allow us to capture data on safety and tolerability, functional status, QoL, and global impression of change. The collection of data from these outcome measures will support the study's goal of evaluating the overall impact of cannabis-based medicines for symptom management in PALS.

CLT-08: Clinical Experience with Intrathecal NurOwn Cell Therapy in an Outpatient Setting

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Background:
Brainstorm is conducting a randomized (1:1), placebo-controlled Phase 3 clinical trial of NurOwn® in 200 ALS patients in the US. Study participants receive 3 intrathecal doses of NurOwn® or placebo two months apart. NurOwn® is an autologous cellular therapy administered intrathecally (IT) into the ALS patient's spinal fluid in the lumbar region (by lumbar puncture) to enable efficient delivery of the neurotrophic factors' cargo and immunomodulatory cytokines directly into the CNS compartment. As of July 2020, all study participants had completed dosing.

The phase 3 clinical protocol initially required a 24-72 hour post-treatment inpatient hospitalization for observation. This observation period mimicked the post-treatment safety procedures used in prior open label and phase 2 randomized clinical trials of NurOwn®.

With the onset of the COVID-19 pandemic, to reduce hospital resource utilization and participant risk of exposure to COVID-19, the protocol was amended to allow site investigators to discharge participants six hours following the intrathecal therapy.

Methods:
We describe the safety and adverse events in the post-treatment observation period for participants. We will use summary statistics to describe the post-treatment observation period for all trial participants, and separately characterize the post-treatment period for those followed for only six hours, "outpatient follow-up."

Results:
There were 189 participants who underwent 518 intrathecal treatment procedures with inpatient follow-up. A small percentage of these participants underwent treatments with outpatient follow-up.

Discussion:
The participant and investigator experience with intrathecal administration of NurOwn® both inpatient and outpatient setting will be important for future treatments.

Funding:
Brainstorm Cell Therapeutics; Phase 3 Clinical trial was funded by CIRM

CLT-09: I AM ALS presents ALS Signal: A unique tool created by patients and caregivers to educate the ALS community about global ALS clinical trials

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Live Poster Session A, December 9, 2020, 5:10 PM - 5:50 PM

Background:
Advances in neuroscience have led to an increased number of clinical trials available to ALS patients. However, patients are often either not informed of these trials or advised to search for clinical trial opportunities on their own. This can lead to patients not enrolling in trials as registries can be challenging to navigate or provide limited information. To remedy this, a team of patients and caregivers from I AM ALS' Promising Therapies and Clinical Trials teams created a clinical trials dashboard that brings together disparate information and presents opportunities in a digestible manner.

Objective:
According to the 2019 survey of 551 ALS patients conducted by Ipsos on behalf of I AM ALS, 30% of ALS patients either did not know about clinical trials or did not know how to find information on clinical trials(1). To address this, I AM ALS volunteers sought to create a unique patient-centric dashboard to educate the ALS community about global therapeutic interventional trials to create more informed patients and to increase trial participation.

Methods:
I AM ALS Clinical Trials community team members reviewed international registries for current and upcoming clinical therapeutic interventional ALS trials. The team debated which specific trial information was of most interest to ALS patients and caregivers and collected this information for each active and upcoming trial. The data was compiled within a spreadsheet, which was exported to create a dashboard containing ten clinical trial filters to customize search functions. A U.S. trial finder was developed within the dashboard with five additional filters to help people find trials near them. The I AM ALS Scientific Advisory Council, patients, caregivers, clinician-scientists and other stakeholders reviewed the dashboard's content and format prior to publication.

Results:
I AM ALS introduced ALS Signal: A Clinical Trials Dashboard to the ALS community on July 25, 2020 and is available at https://iamals.org/alssignal/. ALS Signal had a total of 6,450-page views between July 25 and September 24, 2020. Currently, the dashboard contains 80 clinical trials with 73 trials listed on clinicaltrials.gov and seven trials from other registries.The dashboard is a living document. Updates are made at least every two weeks to reflect new information from registries, press releases and correspondence with sponsors and researchers.

Discussion:
The creation of a centralized dashboard with filters, a rating system and a trial finder allows patients and caregivers an opportunity to personalize their search for clinical trials.The goal of this dashboard is to provide hope and facilitate discussions between patients and their health care providers. This tool also benefits researchers, sponsors and advocacy organizations wishing to increase trial participation and educate and empower patients.

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CLT-10: Oral Suspension Formulation of Edaravone for Amyotrophic Lateral Sclerosis: Human Pharmacokinetics and Development Plan

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Background:
An intravenous (IV) formulation of edaravone is approved for use in amyotrophic lateral sclerosis (ALS) in Japan, South Korea, the United States, Canada, Switzerland, China, and Indonesia. An investigational oral suspension formulation of edaravone is being developed as a potentially more convenient formulation for ease of administration.

Hypothesis:
Pharmacokinetic (PK) studies and Phase 3 studies are expected to help provide the data needed to seek registration for marketing authorization pending further discussion with health authorities.

Methods:
A Phase 1, dose-ranging PK study was conducted in Japanese and Caucasian healthy volunteers. A PK bioequivalence bridging study was also completed. This will be followed by a Phase 3 study in patients with ALS.

Results:
A single oral suspension dose of approximately 100 mg of edaravone appeared to deliver Cmax and AUC values comparable to that of the approved 60 mg/60 min IV infusion. Similar PK profiles were found for Japanese and Caucasian subjects. No significant safety findings were observed following single doses of up to 300 mg of oral edaravone.

The safety and tolerability of oral edaravone in dosing cycles the same as the approved IV formulation will be assessed in a single arm, multi-center, open-label, 48-week, Phase 3 study in 150 adult patients with ALS. The efficacy and safety of daily dosing of oral edaravone will be compared to that in the dosing cycles in an additional double-blind, Phase 3b global study in patients with ALS (N≈400). PK data and study designs will be presented on the congress poster.

Discussion:
The completion of initial clinical studies in the oral edaravone development plan is intended to help establish the data needed to seek registration for marketing authorization pending further discussion with health authorities.

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CLT-11: Patient-centred priorities for participation in longer-term ALS studies: Improving enrollment and retention

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Background: Research projects in the ALS community are challenged by low enrollment[1] and, particularly for longer-term projects, high attrition.[2] Meaningful patient engagement improves study enrollment and retention.[3] To prepare for CAPTURE ALS (The Comprehensive Analysis Platform To Understand, Remedy and Eliminate ALS), a long-term, open-science research study and biorepository initiative, we asked ALS patients and family caregivers about recruitment and research protocols.

Objectives: To identify patient-centred priorities for participation in research.

Methods: Participants were recruited from the ALS Talk Project, an asynchronous, moderated focus group study using the online itracks™ platform. Polls and open-ended questions were available for 14 days. Topics included: preferences for communication about research opportunities; motivation to participate in long-term, non-intervention studies; barriers and incentives for participation in longer-term studies; what studies might 'give back' to participants; and views on data-sharing across jurisdictions and with pharmaceutical companies. Qualitative data was exported in NVivo 10™ and inductively analyzed using directed content analysis and the constant-comparative approach.

Results: Eighteen ALS patients and 14 caregivers from three Canadian provinces participated. We identified three primary themes. (1) Research as partnership. Research participation gives people a sense of purpose, especially if they feel like "partners in finding out more about ALS." Before participating, they want to "know everything about the study." Throughout participation, interaction with healthcare professionals/researchers – including face-to-face, email, formal presentations, webinars and/or Q&A sessions – is highly valued. (2) Practicality is important. Participants want assessments in their homes or communities to facilitate ongoing research participation as physical capabilities and life priorities change. Participants value receiving copies of personal data and/or assessment results. (3) Data-sharing is necessary. Despite reservations, most participants were willing to share anonymized data with both academic researchers and pharmaceutical companies. Participants want assurance of privacy and data-security from healthcare professionals/researchers.

Discussion: This study investigates the priorities of ALS patients and family caregivers who are considering research participation. Research protocols should be designed to explicitly demonstrate value for participants as research partners and to accommodate practical patient needs. Ongoing communication with researchers throughout longer-term studies, including opportunities to learn more about ALS and research, is validating and may motivate retention. ALS patients and caregivers recognize that data-sharing is critical to improving ALS knowledge and, ultimately, developing treatments. Better understanding of patient and caregiver priorities will enable patient-centred design and foster successful research. Findings have implications for recruitment, retention, and data-sharing in ALS research.

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CLT-12: Could both SNIP and TCCO2 replace FVC as an eligibility criteria for ALS clinical trials? A retrospective chart review.

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Live Poster Session B, December 10, 2020, 5:10 PM - 5:50 PM

Background:
Forced Vital Capacity (FVC) is currently the pulmonary function test (PFT) most commonly used as an exclusion criteria in amyotrophic lateral sclerosis (ALS) clinical trials (Paganoni 2014), as the appearance of respiratory failure symptoms correlates with a poor prognosis (Singh 2011, Pierce 2019). This test is hard to perform for bulbar patients as it requires proper sealing of the mouth around the machine (Ackrivo 2019). The other commonly used methods to detect respiratory failure in clinic for ALS patients are the Sniff Nasal Inspiratory Pressure (SNIP) test and transcutaneous CO2 (TCC02) measure, allowing measurement of inspiratory muscle strength and arterial carbon dioxide levels (Pinto 2018, Rafiq 2012).

Objectives:
First, we will describe the association between three measures of PFTs (FVC, TCCO2 and SNIP) through the course of multiple visits.
Second, we will examine whether there is an association between the site of ALS onset (bulbar versus limb) and the rate of decline of the FVC, TCCO2 and SNIP over time after adjusting for demographic and clinical risk factors.
Then, we will examine baseline predictors of the rate of decline of FVC, TCCO2 and SNIP over time using demographic and clinical risk factors.
Finally, we will examine the association of FVC, TCCo2 and SNIP at baseline with tracheostomy free survival.

Methods:
We will perform a retrospective chart review based on the patient population at the ALS Clinic of the Montreal Neurological Institute. FVC, SNIP and TCCO2 are performed as per standard practice at multiple time-points during the course of the patient's progression: at the time of diagnosis, 1 month, 3 months, 6 months and 1 year post-diagnosis, allowing an encompassing picture of the PFT measures evolution during the first year post-diagnosis.

Results:This is a work in progress. Information will be taken from patient's charts and analyzed before being presented.

Conclusions: This is a work in progress. Results from the data analysis will provide greater insight on a possible alternative PFT evaluation for ALS patients, especially for their inclusion into clinical trials.

Acknowledgements:
Montreal Neurological Institute and Hospital

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CLT-13: Design of the Phase 3, Randomised, Placebo-Controlled Trial of oral Arimoclomol in Amyotrophic Lateral Sclerosis ORARIALS-01

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Background:
Arimoclomol is an amplifier of the heat shock response under conditions of cellular stress. Heat shock response promotes clearance of intracellular protein aggregates, natural folding of nascent proteins, and refolding of misfolded proteins, reconstituting normal protein function - actions that are expected to have a disease modifying effect in ALS. In a 12-month phase 2 trial of 36 SOD1 patients with aggressive disease, arimoclomol treatment reduced the rate of ALSFRS-R decline by 0.5 points/month and by 1 point/month in the subgroup of 24 patients with the A4V mutation as compared to placebo (1). Exploratory efficacy assessment of the open label extension part of an earlier phase 2 trial in the broader ALS population, suggested a slower rate of ALSFRS-R decline compared to an historical placebo group (~30% difference in decline, p=0.034) (2).

Objectives:
To present the design of a Phase 3, Randomised, Placebo-Controlled Trial of Arimoclomol in ALS (ORARIALS-01)

Methods:
Inclusion criteria were based on analysis of the PRO-ACT database identifying patients with relatively homogenous progression over an observation period of 12–18 months. Based on survival and changes in ALSFRS-R, it was evident that an observation period of 18 months would allow for more robust signal detection than 12 months with regard to survival. The primary endpoint is the measurement of the Combined Assessment of Function and Survival (CAFS) in the arimoclomol treatment arm as compared to placebo after 18 months. Based on the phase 2 trial an effect size of 0.48 at 18 months is expected, 213 patients randomised 2:1 to arimoclomol or placebo will provide 90% power to detect a statistically significant difference, at a two-sided type-1 error of 0.0446 adjusting for a group-sequential interim analysis. Secondary endpoints include PAV/tracheostomy-free survival and change in ALSFRS-R.

Results:
Eligible participants are patients aged ≥18 years who meet the revised El Escorial criteria for clinically possible, clinically probable, clinically probable laboratory-supported or clinically definite ALS, or have familial ALS caused by a known pathogenic mutation. The patients will be ≤18 months since first appearance of weakness, have a baseline ALSFRS-R ≥35, and a relatively preserved lung function with SVC ≥70% of predicted normal. Participants will be evaluated in clinic every 8 weeks for endpoints, safety measures, quality of life and biomarkers for the first 52 weeks and then every 12 weeks. To reduce the drop-out rate, patients may be assessed in their home if disease progression impacts their ability to attend the trial site.

Discussion and Conclusion:
Details of and justification for the design of the ORARIALS trial and updates on progress will be presented.

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CLT-14: Detectable Effect Cluster (DEC) Analysis: A Novel Machine-Learning Subgroup Analysis Method for Drug Rescue

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Introduction:
ALS drug development has been plagued by high clinical trial failure rates in trials. 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 dataset to predict disease progression is used to rank-order trial participants. An initial 50 subgroups are systematically expanded by adjusting prediction thresholds in 2% nearest-neighbor increments until the full analysis set is reached. To analyze the subgroups, a matrix is plotted in which each block is derived using distinct upper and lower thresholds and a series of analyses are performed that assess variance (RMSE), treatment effect (TE), effect size, and P value, thus developing a series of heat maps that can reveal subgroups with favorable conditions for detecting a significant effect size, whether it be through enhanced TE, lowered variance, or a combination. The method was applied to the Ceftriaxone-ALS (NCT00349622) and Topiramate-ALS (1) data sets available from the NINDS.

Results:
To focus on the development of DEC analysis, we used the 285 patients who remained on study for one 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 to test in a second analysis. We randomly separated the 190 treated patients into two groups, one for the exploratory analysis and a second to test the hypothesis. One-year predictions using our validated percent expected vital capacity model were made for all patients in the analysis set. A broad central region, a “hot spot,” where moderately progressing patients localized was detected and a subgroup, representing predicted one-year decline in percent expected vital capacity between 15% and 25% was selected to determine whether it could be found in the test set. Examination of the test group confirmed the results of the exploratory analysis.
The Topiramate-ALS trial (1) proved useful for developing DEC analysis. In contrast to ceftriaxone, which had a 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.

Conclusion:
DEC analysis provides an unbiased, innovative new framework for re-examining failed ALS drug trials and uncovering ‘hot spots’ where a prediction-defined patient subgroup could form the basis of a subsequent successful trial.

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CLT-15: Factors Influencing Trial Participation in Motor Neuron Disease (FIT-Participation-MND)

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Introduction:
Motor neuron disease (MND) is a rapidly progressive and fatal neurodegenerative disorder with limited treatment options. 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 MND. Historically, neurological 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 [1], terminated trials, or invalid conclusions [2].

Aim: This study seeks to investigate patient-specific factors that affect recruitment and retention of people with MND to MND-SMART. An improved understanding of these factors will improve trial protocol design to optimise recruitment and minimise attrition.

Hypothesis: We hypothesise that patient-specific factors, such as 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:
People with MND who have given prior consent to be contacted on the Scottish MND Register, Clinical Audit Research and Evaluation MND (CARE-MND), will be sent study invitation packs, including an invitation for a caregiver identified by the potential participant. Participants with MND will complete the HADS, PHQ-9, STAI-Y, ALSSQOL-20, CDC-HQOL-4 and a novel study-specific questionnaire to evaluate Attitudes towards Clinical Trial Participation (ACT-Q). Additional clinical data including disease phenotype, cognitive impairment and physical functioning will be extracted from participants' CARE-MND or MND-SMART records. Caregivers will be asked to complete the Brief Dimensional Apathy Scale (b-DAS) regarding the participant's behaviour. 12 months after the final questionnaire pack is returned, we will complete a data request to MND-SMART to evaluate how many participants were recruited into the trial and how many remained involved after 12 months.

Analysis Plan: Descriptive statistics will be used to summarise and compare the scores between assessment tools and the number of participants reaching pre-defined impairment thresholds. Questionnaire results will be grouped for analysis as follows: attitudes, quality of life cognitive impairment, behavioural change, physical functioning, neuropsychiatric and clinical phenotype. To explore the association of these covariates with participation or non-participation in MND-SMART, and with withdrawal within 12 months, we will use univariate and multivariable logistic regression; results will be presented as odds ratio and 95% confidence intervals.

Study Status: Ethical approval was provided by the West of Scotland Research Ethics Committee 3 (20/WS/0067) on 12th May 2020. This study is recruiting at the time of abstract submission.

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2. Gul, R.B. and P.A. Ali, Clinical trials: the challenge of recruitment and retention of participants. Journal of clinical nursing, 2010. 19(1-2): p. 227-233.

CLT-16: I AM ALS presents the Patient-Centric Trial Design (PaCTD) Rating System: A clinical trial rating system to promote more humane and efficient ALS clinical trials.

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Background:
Patient recruitment for ALS drug studies has been a challenge for both the scientific and patient communities. In 2019, Ipsos conducted a survey of 551 ALS patients on behalf of I AM ALS. This survey found that patients were more likely to enroll in phase 3 clinical trials with a lower likelihood of receiving a placebo, reimbursed travel expenses and open label access by 74%, 83% and 91% respectively(1). I AM ALS Clinical Trials Team created the Patient-Centric Trial Design (PaCTD) rating system to highlight clinical trials that fit patient preferences and aligned with the the FDA's 2019 Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry and encourage drug sponsors to use more humane and efficient clinical trial design. This team consists of patient and caregiver volunteers.

Methods:
The I AM ALS Clinical Trials Team created a five-star rating system to assess clinical trial design based on nine design elements of patient centrality, which were grouped into three categories and weighted differently for the overall rating:

1. Optimizing access to investigational therapies (60%). This category addresses whether a trial includes the following elements:
- Open-Label Extension
- Minimizes placebo usage
- Expanded Access Program

2. Advancing scientific progress (30%). This category addresses whether a trial includes the following elements:
- Consideration of disease heterogeneity
- Use of scientifically-justified eligibility criteria
- Investigation of one or multiple biomarkers
- Independent unblinded review panel

3. Focusing on patient-friendly (10%). This category addresses whether a trial includes the following elements:
- Use of run-in observation period
- Reduce travel burden by use of novel methods

Rating criteria were informed by the FDA's 2019 Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry, patients and caregivers and then validated by pharmaceutical industry representatives, neurologists and researchers.

PaCTD ratings do not measure or evaluate the treatment's safety or efficacy.

Results:
As of September, 2020 five ALS clinical trials were evaluated using the PaCTD criterion:

- Brainstorm (NurOwn)
- Orphazyme (Ariclomol)
- Alexion (Ultomiris)
- Biogen (BIIB067 (SOD1))
- Orion Pharma (Oral Levosimendan)

Ratings were discussed in meetings and presented to therapy sponsors before publication for comment. The PaCTD Rating System can be found at https://iamals.org/pactd-rating-criteria/.

Acknowledgements:
We would like to thank patients and caregivers for taking part in the development of the PaCTD criteria.

1. Ispos, Clinical Trials Survey, 2019 (382/450 words)

CLT-17: Impact of Patient Characteristics on Effect Size in FORTITUDE-ALS

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Background:
FORTITUDE-ALS (NCT03160898) was a 12-week, phase 2, double-blind study of reldesemtiv in 458 patients with ALS randomized to 1 of 3 reldesemtiv doses or placebo. Outcome measures included slow vital capacity (SVC), ALS Functional Rating Scale-Revised (ALSFRS-R), and quantitative muscle strength. Although the primary analysis of the weighted dose-response in the change in SVC from baseline to Week 12 did not reach statistical significance (p=0.11), each outcome measure demonstrated a trend toward reduced progression rates with reldesemtiv.

Hypothesis:
Baseline patient characteristics are associated with the magnitude of effect of reldesemtiv versus placebo in FORTITUDE-ALS.

Methods:
Study inclusion required diagnosis ≤ 24 months; symptom duration (SD) was recorded at screening. Subgroup analyses were performed to identify whether baseline characteristics predicted differential treatment effects.

Results:
In general, static measures of disease state (such as baseline SVC and medications at baseline, and bulbar vs. spinal onset) did not predict impact of reldesemtiv. However, patients with faster pre-study ALSFRS-R progression rates showed larger treatment effects. The middle and fastest progressing tertiles of patients combined showed a 27% difference at 12 weeks between the reldesemtiv and placebo arms (1.15 ALSFRS-R points, p=0.011), compared to 18% (0.4 points; p=0.43) in the slowest progressing tertile. In general, patients with longer SD had slower progression; faster progressing patients had shorter SD; 59% of those with SD > 24 months were in the slowest tertile. In addition, the majority of minimally affected patients at baseline (ALSFRS-R ≥ 45) were slow progressors (41/43 in the slowest tertile). In a post hoc analysis, we compared the treatment effect in patients with symptoms ≤ 24 months and a baseline ALSFRS-R score of ≤ 44 to the original primary analysis population in FORTITUDE-ALS. The effect size and its statistical significance increased in this subgroup despite reducing the number of analyzed patients. For all patients randomized (n=458), the change from baseline to Week 12 in the ALSFRS-R total score combining all reldesemtiv-treated patients compared to placebo showed a least square mean (LSM) difference of 0.87 (p=0.013). Limiting the analysis to patients with symptoms ≤ 24 months and a baseline ALSFRS-R score of ≤ 44 (n=272), the LSM difference was 1.84 (p=0.0002).

Conclusions:
The impact of reldesemtiv was more apparent in patients with faster pre-study rates of progression. Short symptom duration and lower baseline ALSFRS-R scores are both correlates of faster progression rate. This is consistent with recent clinical trials in which stringent inclusion requirements limited study populations to early onset, faster progressing patients as slowly progressing patients may contribute little to detecting a treatment effect. Future studies of reldesemtiv in ALS will consider strategies to minimize but not exclude patients with slower pre-study disease progression to increase trial efficiency and sensitivity.

CLT-18: Patient Reported Outcomes and ALS: Characteristics of the Self-Entry ALSFRS-R and the ABC Scale

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Background:
Patient reported outcome measures (PROMs) are emerging as important tools in facilitating clinical care and research in ALS.

Objective:
To compare patient reported outcome measures (PROMs) from routine clinic visits with clinical outcomes and patient reported falls.

Methods:
We analyzed PROM and clinical data collected on patients presenting for follow-up visits at an ALS Multidisciplinary clinic over a two-year period. The PROMs included the patient-facing ALSFRS-R ("self-entry ALSFRS-R"), ABC, and a question about fall history. Clinical data included the ALSFRS-R completed in clinic by a certified evaluator ("standard ALSFRS-R").

Results:
449 patients filled out at least one PROM, 183 had both self-reported and standard ALSFRS-R scores from the same visit, and 49 had these data from two visits, allowing longitudinal comparison of ALSFRS-R methods. Cross-sectional standard versus self-entry ALSFRS-R total scores had high agreement (ICC = 0.81, 95% CI= 0.67, 0.88). Self-entry ALSFRS-R total scores were significantly higher than standard ALSFRS-R scores (2.3, SD= 4.5, paired t-test p< 0.001). In the longitudinal dataset, the average rate of decline were not significantly different in self-entry and standard ALSFRS-R. ABC scores had high correlations with the self-entry and standard ALSFRS-R Gross Motor subdomain scores (Pearson r=0.76, p<0.001 and Pearson r=0.72, p<0.001, respectively). ABC score was negatively correlated with the number of reported falls within the last month (spearman r= -0.4; p<0.001).

Discussion:
In a multidisciplinary clinic setting, self-entry and standard ALSFRS-R scores were similar, but not interchangeable, given the bias toward higher scores with self-entry. Rates of changes were not significantly different in this study, but more data is needed to fully assess this. The ABC score was also negatively correlated with reported fall history. These results demonstrate that the ABC scale holds promise as a PROM useful for clinical care and research in ALS. In an era of increasing opportunity to collect PROMs, and during the COVID-19 pandemic, in which remote data collection is essential to continuing clinical trials, these outcomes may have practical advantages over outcomes collected in clinic.

CLT-19: Randomized clinical trials in Amyotrophic Lateral Sclerosis: current issues and possible solutions

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Background:
Success rate of randomized clinical trials (RCTs) for finding a treatment for Amyotrophic Lateral Sclerosis (ALS) is disappointingly low, also due to the absence of a homogeneous set of inclusion criteria and to a high mortality rate of included patients. The new guidelines for RCTs suggest using broader inclusion criteria and stratifying patients for the most relevant prognostic factors.

Objective:
We aimed at computing mortality rates of ALS patients during a simulation of an RCT, depending on forced vital capacity (FVC) and time interval between disease onset and trial entry, and analyzing which prognostic factors should be considered for recruitment.

Methods:
We selected the first spirometry of ALS patients included in the PARALS Registry, diagnosed from 1995 2000 to 2016, performed during 4 time intervals from disease onset: 6-12 months (group 1; 453 patients); 12-18 months (group 2; 405 patients); 18-24 months (group 3; 272 patients); 24-36 months (group 4; 263 patients). The date of spirometry corresponded to trial entry. For each group, mortality rates were computed at 3,6,9,12,18,24 months from trial entry. Risk for death/tracheostomy was computed using Cox proportional hazards models, adjusted for the most relevant prognostic factors. Patients were further stratified in normal (NPs, ΔALSFRS <1.1) and fast progressors (FPs, ΔALSFRS ≥1.1). Median survival from trial entry was calculated depending on FVC% value at recruitment. Finally, patients were considered together and the first spirometry for each patient was included: Cox proportional hazard models were used to investigate if risk factors were different between NPs and FPs.

Results:
As the time interval from disease onset to trial inclusion increased, patients were younger, the number of women raised, median FVC% values, and the proportion of FPs decreased. The risk for death/tracheostomy increased at reducing FVC% values (p <0.001). Mortality rates decreased with the increase of time interval between onset- and recruitment, likely due to the progressive reduction of FPs patients. FPs represented 21.1% of all patients with a risk for death/tracheostomy increased by 53.8%. The only prognostic factors for FPs were FVC% and use of NIMV (HR 0.991, p<0.001 and HR 0.618, p=0.001, respectively). Median survival was >1 year for FPs with FVC% >80.0% and for NPs with FVC% >60%.

Conclusions:
Stratifying patients in prognostic categories is essential for RCTs, mostly depending on disease progression rate and pulmonary function. Trial entry for FPs should be accelerated increasing the chance of having a good pulmonary function.

CLT-20: 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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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 to 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. In support of this, 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. 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 seems to delay the deterioration of motor function, when assessed by multiple locomotive and neurological criteria. Additionally, in human 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. These findings suggest that the effects of enoxacin on miRNA levels have the potential to impact the expression of key proteins involved in the pathogenesis of ALS. Collectively, these preclinical data support the testing of enoxacin as a disease-modifying therapeutic for familial and sporadic ALS.

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) in adults with ALS (36 subjects in total and 12 subjects per 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.

CLT-21: Plasma exchange with albumin replacement slowed amyotrophic lateral sclerosis disease progression. A pilot study

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Background:
Plasma exchange (PE) is an extracorporeal blood purification process that removes substances from the blood. In this study, albumin was administered as the replacement fluid. In addition to maintaining oncotic pressure, albumin has additional antioxidant and anti-inflammatory properties. PE is a well-tolerated procedure that has been used to treat several other neurological conditions including Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy.

Aim:
The goal of this study was to evaluate the effect of PE with albumin replacement on disease progression in patients with ALS.

Methods:
This was an open-label, uncontrolled, single-arm, single-center, pilot study. Men and women aged 18 to <70 years with a definite, possible or probable diagnosis of ALS according to El Escorial/Airlie House criteria, and had a forced vital capacity (FVC) >70% of predicted value were eligible to participate in this study. Patients underwent 6 months of PE-treatment with 5% albumin (Albutein® 5%) replacement in two phases: one intensive phase involving two PE sessions per week for three weeks, followed by a maintenance phase involving one PE session per week for 21 weeks. The follow-up period after treatment was 6 months.

Endpoints were changes in the ALS Functional Rating Scale-Revised (ALSFRS-R) score and FVC. Based on the typical survival of 3-5 years from the onset of ALS symptoms, and a typical decrease of 1 point/month in the ALSFRS-R overall score, three categories of disease progression were defined: "normal", "slow", and "fast". These categories depended on the ALSFRS-R slope. Between –0.8 and –1.33 points/month was "normal", < –0.8 points/month was "slow", and > –1.33 points/month was "fast".

Results:
Thirteen adults with ALS were enrolled and evaluated. Median (IQR) overall ALSFRS-R score at baseline was 42.0 (37.0, 44.0). ALSFRS-R scores declined throughout the study, although the median decline was less than expected in pre-treated patients. Seven patients had a slower decline than expected at the end of treatment and five patients had a slower decline at the end of study. Six patients remained in the same baseline slope progression category while four improved their slope category at the end of treatment. Median (IQR) of FVC and predicted FVC percentage at baseline were 3.9 (3.0, 4.9) L and 87.0% (76.0, 96.0), respectively. Median FVC decreased significantly during the study. The study treatment was well-tolerated.

Conclusion:
PE with albumin replacement was safe and well-tolerated in ALS patients. Although functional impairment progressed, most patients showed a slower than expected rate of decline at the end of treatment. In terms of ALSFRS-R slope progression, most patients had an unaltered (54.5%) or reduced slope progression (36.4%).

CLT-22: PrimeC as a Promising Treatment for ALS

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NeuroSense Therapeutics is a biotech company, developing a drug for ALS. The drug, named PrimeC, is a novel formulation composed of unique doses of ciprofloxacin and celecoxib, which aim to simultaneously target several pathological mechanisms of ALS, including dysregulation of microRNAs (miRNAs), iron accumulation and neuroinflammation.
Dysregulated miRNAs are found in ALS model's and in patient's microglia cells, motor neurons and skeletal muscles. miRNAs control multiple molecular mechanisms such as neuroinflammation, synaptic formation, neuronal activity and differentiation. Furthermore, studies showed that reduction in miRNAs was sufficient to cause spinal motor neuron degeneration in vivo.
In addition to being a broadly used fluoroquinolone antibiotic, ciprofloxacin has been shown to be a potent iron chelator, as well as a regulator of Dicer activity, a key enzyme in the miRNA processing pathway. It can also indirectly hinder neuroinflammation.
Celecoxib, an NSAID, is a known COX-2 inhibitor. However, it is known to have additional activities that are COX-2-independent. Although celecoxib has not historically shown benefit for ALS patients when given at high doses as a single agent, low doses were shown to be effective in pain, and played a synergistic role with ciprofloxacin in regulating oxidative stress and inflammation in murine brain abscesses.
In recently published pre-clinical studies, ciprofloxacin and celecoxib, separately and in combination, were tested in two models of ALS zebrafish. Only the combination, at certain doses, showed significant effects on behavioral and morphological outcomes. In a SOD1 model, it caused an elevation of ~84% in the fish swim distance and elicited recovery of both impaired motor neuron morphology and abnormal neuromuscular junction structure. Furthermore, it preserved the ramified morphology of microglia cells in these fish. In a TDP-43 model, mutant fish treated with the combination exhibited significantly longer swim distance (110%) and velocity (~44%).
Our results suggest a synergistic effect between ciprofloxacin and celecoxib by a yet unknown mechanism. One explanation may be supported by the fact that celecoxib inhibits MDR1, which can lead to accumulation of ciprofloxacin in cells. This may be further supported by studies that showed elevation of CSF ciprofloxacin levels by co-administration of COX inhibitors.
The synergism observed in our preclinical zebrafish studies strongly indicated that PrimeC acts as a neuroprotector, and justified further testing it in ALS patients.
Therefore, two small clinical studies in ALS patients are currently running in Israel and the US, in order to evaluate the safety and primary efficacy of PrimeC. Interim, 6-month results from these studies, showed that PrimeC was safe and well tolerated and importantly, exhibited extremely encouraging trends in key parameters, including ALSFRS-R and FVC.

CLT-23: RESCUE-ALS Trial, A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of CNM-Au8 to Slow Disease Progression in Amyotrophic Lateral Sclerosis Patients: Design and Interim Blinded Results

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Live Poster Session B, December 10, 2020, 5:10 PM - 5:50 PM

Background:
RESCUE-ALS is a novel Phase-2 clinical trial investigating the new therapeutic, CNM-Au8 in patients with recently-diagnosed sporadic ALS. Here we present the rationale, study design, and interim blinded efficacy data. CNM-Au8 is an aqueous suspension of clean-surfaced, faceted gold nanocrystals with catalytic activity that has been shown to enhance neuronal metabolic energy, reduce oxidative stress and enhance protein homeostasis.

Hypothesis:
By employing electromyography (MUNIX), a sensitive, quantitative measure of
motor neuron loss, we will detect therapeutic effects of orally administered CNM-Au8 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 ALS
patients. Participants will be randomized 1:1 to receive 30 mg of CNM-Au8 once daily or
matching placebo over a 36-week double-blind treatment period. Efficacy will be assessed as the average change in motor neuron number as estimated by electromyography (MUNIX) for the ADM, APB, BB, and TA. Secondary efficacy endpoints include MScanFit, MUSIX, Split Hand Index, and Neurophysiology Index. Exploratory endpoints include clinical safety and quality of life assessments.

Results:
Trial design and baseline characteristics of participants will be presented. Despite the current pandemic, this trial was enrolled with 43 participants as of September 2020. Baseline characteristics include [mean (SD)], MUNIX(4) score: 92 (47.3); FVC % predicted: 80.5 (16.4); ALSFRS-R: 38.5 (6.1); ALSSQOL-20: 3.3 (1.3), mean time from diagnosis: 4.8 (4.6) months; riluzole background treatment: 86%. Interim, blinded MUNIX(4), FVC, and ALSSQOL-20 results will be presented. Preliminary analyses of blinded data from all study participants show less MUNIX(4) decline than previously published studies (Neuwirth et al JNNP 2015).

Discussion:
As the first therapeutic nanocatalyst in development for neurodegenerative diseases, CNM-Au8 has a unique multi-modal mechanism of action that addresses disease-related bioenergetic failure, oxidative stress, and proteostasis dysregulation. CNM-Au8 is not metabolized or degraded as a result of its catalytic activity, which is maintained until excretion. It is orally bioavailable and crosses the blood brain barrier. A successful outcome of this study establishes the direct treatment of cellular bioenergetic failure as a therapeutic target for ALS and supports the validation of using electromyography endpoints as biomarkers for ALS disease progression.

CLT-24: A new prospective study to investigate the natural history of primary lateral sclerosis for future clinical trials: the PLS Natural History Study (PNHS)

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Live Poster Session C, December 11, 2020, 12:05 PM - 12:50 PM

Background: Primary lateral sclerosis (PLS) is a rare and pure upper motor neuron (UMN) disease. There is considerable increased scientific interest in PLS recently. The Second International PLS Conference was held in 2019. The PLS functional rating scale (PLSFRS) (Mitsumoto et al. 2020) and New PLS Diagnostic Criteria (Turner et al. 2020) were recently published. Clinical trials for PLS will require better knowledge of the disorder's natural history

Objectives: To define the natural history of "early" and well-established PLS cases and to validate the NPDC.

Methods: Fifty participants with Early PLS including Probable PLS (defined by the New Diagnostic Criteria as 2 to 4 years following symptom onset) and in addition, individuals with UMN disease for less than 2 years following symptom onset, and 50 participants with Definite PLS (defined by the New diagnostic Criteria as more than 4 years following symptom onset but excluding those exceeding 15 years) will be enrolled based on strict inclusion and exclusion criteria from 34 US and Canadian sites. The PLSFRS* is the primary outcome. Secondary outcomes include physical exams, cognitive testing*, medication and durable medical equipment use*, Penn UMN scale, %FVC, timed up and go (TUG) testing, Amyotrophic Lateral Sclerosis-specific quality of life-short form (ALSSQOL-SF)*, Neuro-QOL*, diadochokinetic "pa-ta-ka" repetition*, and finger and foot tapping*. Tests* will be conducted via televisits. Visits at baseline and at Months 6 and 12 require in-person site visits. Visits at Months 3, 9, and 24 will be televisits (*), including the PLSFRS. A needle electrode EMG will be performed at Month 12. DNA analyses will include C9 repeats, and familial ALS, HSP, and PD pathogenic mutations to exclude known definable causes for PLS. Urinary isoprostane and 8-oxodG will be measured. Urine and plasma samples, including DNA, will be stored in the NIEHS Biorepository. All data will be managed by NeuroBANK. We will analyze the data using generalized linear mixed effects models to estimate rate of disease progression, to examine differences between the two patient cohorts, and to account for participant characteristics.

Conclusion: The PNHS will begin enrollment soon, and should provide novel insights into the clinical course of PLS. We hope this study will facilitate the conduct of meaningful PLS clinical trials.

Acknowledgements: Mitsubishi-Tanabe Pharma (MTP), ALS Association, and the Spastic Paraplegia Foundation (SPF) are funding the study. Members of the Steering Committee include: YKK Cheung, KD Dave, MK Floeter, A Genge, M Gilmore, D Marren, H Mitsumoto, S Paganoni, A Sherman, and Z Simmons.

CLT-25: A Phase 1, Multicenter, Open Label, Single-Ascending Dose Study to Evaluate Safety, Tolerability, and Pharmacokinetics of AP-101 in Familial and Sporadic Amyotrophic Lateral Sclerosis (ALS)

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Mutations in SOD1 result in misfolding of the SOD1 protein. This was the first genetic variant associated with ALS. Misfolding of SOD1 also occurs in the absence of mutation. Mis-folded SOD1 can be detected in the majority of ALS patients suggesting that SOD1 is a common pathogenic driver across familial and sporadic forms of ALS. AP-101 is a fully human IgG1 antibody with high affinity and selective binding to pathogenic misfolded SOD1 protein. In transgenic mouse models of ALS, a murine version of AP-101 was able to attenuate loss of spinal cord motor neurons and motor function as well as prolong overall survival.

Given the rapidly fatal nature ALS and the high unmet need, an efficient accelerated dose escalation study was performed using an open label oncology style 3+3 design (ClinicalTrials.gov Identifier: NCT03981536). Specifically, AP-101 was administered to patients via intravenous infusion over 1 hour at increasing dose levels of 100, 500 or 2500mg. At each dose level, a sentinel patient was observed before recruitment of two additional patients into the cohort. After observation for 3 weeks and in the absence of any drug related toxicity the next dose cohort was opened for recruitment. If any safety signal was observed in the first 3 patients, an additional 3 patients would be recruited at the same dose level. Dose limiting toxicities in 2 or more patients at any dose level would result in a declaration of maximum tolerated dose. The overall goal was to assess safety, tolerability, and pharmacokinetics of AP-101 after intravenous administration in fALS and sALS patients. Cerebral spinal fluid was also collected from patients

To date, no dose-limiting toxicities effects or any safety or tolerability concerns related to AP-101 have been observed. The most common adverse events are related to the lumbar puncture associated with patient screening. Results will be used to guide the design of a proof-of-concept study to examine the efficacy potential for AP-101.

CLT-26: A Phase II Clinical Trial of Perampanel for Sporadic Amyotrophic Lateral Sclerosis

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Background: Perampanel, a non-competitive α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor antagonist, arrested disease progression in a sporadic ALS (SALS) mouse model, suggesting its potential use in humans.

Objectives: To evaluate the efficacy and safety of perampanel at daily doses of 4 mg and 8 mg, compared with placebo, in patients with SALS.

Methods: This multicenter, double-blind, randomized, placebo-controlled, phase 2 study was conducted at 12 sites in Japan. Patients with probable or definite ALS as defined by revised El Escorial criteria were enrolled. Using a computerised interactive system with the following minimization factors: change in ALSFRS-R score during the observation period, sex, age, and the use of riluzole or edaravone, patients were randomly assigned in a 1:1:1 ratio to receive placebo, 4 mg perampanel daily, or 8 mg perampanel daily. The primary efficacy outcome was the change in ALSFRS-R scores after 48 weeks of treatment. All patients in the intention-to-treat population were analysed. Patients and investigators were masked to treatment assignment.

Results: Between April 2017 and January 2020, 65 patients were randomized to perampanel 4 mg (n=22), 8 mg (n=21), or placebo groups (n=22). There was a significant difference (−8.4 [95% confidence interval −13.9–−2.9]; p=0.015) between the placebo and the perampanel 8 mg group, primarily due to worsening of the bulbar subscore in the perampanel 8 mg group. Changes in MMT grading from baseline to week 48 showed no significant difference among the three groups except that the deterioration in MMT grading of the hamstring muscles on the left side was significantly smaller in the 8 mg perampanel group than in the placebo group. Serious adverse events were significantly more frequent in the perampanel 8 mg group than in the placebo group (p=0.0483). The most common event was dysphagia requiring gastrostomy.

Discussion: Perampanel did not prevent the decline of ALSFRS-R scores in patients with SALS after 48 weeks in a dose-related fashion probably because of significant decline in the bulbar subscore in the high-dose group. Since there was a favourable effect of perampanel on some muscles of the lower extremities as well as considerable variability of change in the ALSFRS-R score after 48 weeks from baseline among the individuals in each group, including virtually non-progressive participants in the perampanel groups, the clinical benefit of perampanel in perampanel-responsive SALS patient needs further study.

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CLT-27: Clinical trials in amyotrophic lateral sclerosis: a systematic review

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Background:
decades of clinical trials, there remains a pressing unmet need for effective treatments for amyotrophic lateral sclerosis (ALS). We reviewed past and present ALS clinical trials to understand the methodological challenges in trial design and delivery.

Methods:
Trial registry databases including clinicaltrials.gov, International Clinical Trials Registry Platform, European Union Clinical Trials Register, and PubMed were systematically searched to identify Phase II, Phase II/III and Phase III Clinical Trials of Investigational Medicinal Products (CTIMPs) assessing potential disease modifying treatments in ALS. Trials registered, completed or published during 2008-2019 were included.

Results:
125 CTIMPs, evaluating 76 drugs, involving 15647 people with ALS (pwALS) were reviewed. Ten drugs were tested in three or more trials. Trials employed predominantly traditional two-arm designs; only 12 used novel designs. Median number of participants was 86. 40% of trials had an attrition rate ≥ 20%. There was a wide variation of primary outcome measures and primary endpoints used.

Conclusion:
Historically, limited participation of pwALS in trials, resources and outcome measures hindered definitive and timely evaluation of drugs in two-arm trials. We propose that future trials will need to be more flexible, scalable and acceptable to all stakeholders.

CLT-28: IC14 in ALS: Expanded Access Program (EAP)

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Background:
IC14 is a chimeric, anti-CD14 monoclonal antibody that may decrease neuroinflammation by improving T-regulatory (T-Reg) cell function. A previous trial (ALS01, Implicit Bioscience Ltd.) of ten ALS participants receiving four doses of IC14 over 4-5 days demonstrated initial safety. We designed an intermediate-size EAP of nine participants (seven enrolled thus far) with ALS receiving IC14 to learn more about safety, pharmacokinetics (PK), and pharmacodynamics (PD).

Methods:
Participants could receive intravenous infusions of IC14, every two weeks for up to a year. 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 functional rating scale revised (ALSFRS-R), slow vital capacity (SVC), and physical, neurologic, and ophthalmologic exams. Whole blood was collected to determine monocyte CD14 receptor occupancy (RO) and T-Reg function; serum was collected to determine phosphorylated neurofilament heavy chain (pNfH) levels and anti-drug antibodies (ADA).

Results:
Participants received IC14 up to 31 weeks (average exposure: 24.9 weeks, range: 11-31 weeks). IC14 was well tolerated. One participant terminated after 28 weeks due to ALS progression. The most commonly reported adverse events (AEs) were falls (n=11) and headaches (n=8); all deemed unrelated to IC14. Treatment-emergent AES (TEASs) deemed probably related to study drug were tongue paresthesias (n=1) and systemic exhaustion (n=1). There were six unrelated serious adverse events (SAEs): bilateral pulmonary emboli (n=1), deep vein thrombosis, fever of unknown etiology (n=1), pneumonia (n=1), and worsening dysphagia (n=2). There were no significant changes in vital signs, exams, or safety labs. CD14 RO increased for all participants after infusion with IC14, with sustained RO of ≥ 80% noted typically after the second infusion, when infusions were administered 14 days apart. In four participants, serum pNfH levels decreased after baseline, two had an increase in pNfH levels, and data for one participant is pending. We observed a significant increase in T-Reg suppressive activity from 31.91% to 63.43% over six doses in one participants and 22.16% to 36% in three doses in another. ADA was undetected in five participants that received up to nine IC14 infusions over 17 weeks.

Conclusion:
IC14 infusions were safe with no significant changes in laboratory tests, vital signs or ophthalmologic examinations when administered for up to 31 weeks. IC14 was successfully administered at home during the COVID-19 pandemic. TEAEs were uncommon, mild, and self-limited. RO data suggest that ideal dosing frequency is likely every 14 days, although personalized titration based on RO might be needed. Preliminary but encouraging data suggest that CD14 neutralization improves T-Reg suppressive function. Data collected in this EAP helped inform the design of a planned randomized clinical trial of IC14 in a larger cohort of people with ALS.

CLT-29: Multiple BM-MSCs (Lenzumestrocel) treatment in patients with amyotrophic lateral sclerosis: Rationale and design of phase III clinical (ALSUMMIT) trial.

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Background:
Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by selective and progressive loss of motor neurons. There is no effective therapeutic regimen for ALS. Stem cell therapy is a promising treatment strategy in patients with ALS. Two repeated treatments with intrathecal autologous BM-MSCs (26-day interval) showed therapeutic benefit lasting at least 6 months with safety in patients with ALS in the previous phase 2 clinical trial.
Objectives: This phase 3 clinical trial (ALSUMMIT) protocol was developed to evaluate and confirm the efficacy and long-term safety of repeated BM-MSCs (Lenzumestrocel) treatment.

Methods:
ALSUMMIT is a double-blind, randomized, placebo-controlled, multi-center, parallel, phase III study for ALS subjects with ALSFRS-R score progression rate of 0.52~1.55 point per month in a 17-week lead-in period prior to administration. The 115 subjects will be randomized as 1:2:2 for study group 1(twice administration of study drug at 26-day interval), study group 2(twice administration at the 26-day interval and then, study drug again three times at 3-month interval), or control group and have an extended 56-week treatment period compared to phase 1/2 clinical trial that had a 24-week study period. The primary efficacy is evaluated by comparing the Joint rank score, which can assess the function and survival of ALS subjects at 12 and 6 months after the 1st administration. Safety assessment will be checked throughout the study. Additionally, after a 56-week main study, a long-term follow-up observational study will be conducted for evaluating long-term efficacy and safety.
Conclusions: ALSUMMIT protocol was recently approved by FDA. This large-scale phase 3 trial will allow determination of the long-term efficacy and safety of multiple BM-MSCs (Lenzumestrocel) treatment for 36 months.

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CLT-30: Optimal therapeutic strategy of autologous MSC treatment for patients with ALS

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Background:
Based on our previous phase I/II clinical trial data, two repeated treatment with intrathecal autologous BM-MSCs (1×106 cells per kg with a 26-day interval) showed therapeutic benefit lasting at least 6 months with safety in patients with ALS. A plausible action mechanism is that BM-MSCs mediate switching from pro-to anti-inflammatory conditions. The decline of ALSFRS-R was significantly reduced in the MSC group in comparison to the control group after 6-month follow-up. The inverse correlation of TGF-β1 and MCP-1 levels i.e., the higher TGF-β1 with lowered level of MCP-1 after the BM-MSCs therapy was noted in the good-responder, which could be potential biomarker to predict effectiveness. Despite the positive effect on ALSFRS-R lasting at least 6 months, the lack of long-term survival benefit may be associated with two limited injections. And, therapeutic effect would not persist long-lasting because BM-MSCs gradually disappear over time in CSF. Considering the immune modulatory effect of BM-MSC treatment using less-invasive procedures, serial additional BM-MSC treatments after one cycle treatment protocol could improve long-term efficacy.

Objective:
To determine optimal time point for additional MSC treatment, serial ALSFRS-R score and CSF biomarkers were systematically analyzed in post-marketing surveillance data.

Methods:
In this study, 99 ALS patients who treated at least 2 times of BM-MSC treatments were enrolled until April 2020. We analyzed inflammatory cytokines in remnant CSFs to show the immune-inflammatory changes of CSF cytokines as well as neurofilaments to reflect axonal injuries in ALS patients.
To evaluate longitudinal CSF biomarker changes, 25 patients who could collect CSF months after a cycle of treatment were analyzed. CSF cytokine levels before and after the treatment are compared. Because of variable follow-up months after treatment, 25 patients were divided into 3 groups depending on the intervals (4 or less months, 5 to 8 months, 9 or more months) and were analyzed to show pre-/post-treatment CSF cytokine changes. Finally, CSF samples from 15 patients with booster injection were analyzed to show longitudinal CSF cytokine changes after booster injection.

Results:
The patients with BM-MSC treatment showed the changes of inflammatory cytokines after the treatment. These changes tended to shift to the baseline months after treatment but differed from the lengths of follow-up interval after a cycle of BM-MSCs treatment. After booster BM-MSC treatment, CSF cytokine were changed as were after 1st BM-MSC treatment.

Conclusion:
Shorter booster treatment intervals after a cycle of BM-MSCs suggested to maintain more prominent changes of CSF cytokins after BM-MSC treatment in ALS patients. Based on these findings, Phase 3 clinical trial (ALSUMMIT) protocol were developed and recently approved by FDA. ALSUMMIT study will allow determination of the long-term efficacy and safety of multiple BM-MSCs (Lenzumestrocel) treatment.

CLT-31: Phrenic nerve study as inclusion criterion and outcome in clinical trials for amyotrophic lateral sclerosis

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Introduction:
Respiratory tests are fundamental for monitoring respiratory function in ALS, and essential in clinical trials. Slow vital capacity (SVC) was cancelled in some countries to prevent SARS-Cov-2 transmission. We aimed to test phrenic nerve motor responses as an option to SVC in clinical trials.

Methodology:
Patients followed-up in our unit were selected respecting inclusion criteria used elsewhere: possible/probable/definite disease; onset-age 18-80 years; disease duration ≤24 months; body mass index (BMI) >20kg/m2; respiratory subscore of the revised ALS functional rating scale (ALSFRS-R) ≥11; upright SVC ≥70%. We added normal phrenic responses (meanPhrenAmpl, ≥0.4mV). All patients were on riluzole. SVC and meanPhrenAmpl were recorded at study entry (T0) and 24 weeks later (T1). Decays were determined. Sample size was calculated for a treatment effect of 30% on the decay rate.

Results:
We included 317 ALS patients (191 males, 225 spinal-onset), mean onset-age 59.9±10.7 (31-80) years, mean onset BMI 25.48±3.2 (20.1-35) kg/m2, mean disease duration 10.5±5.6 (1-24)months, mean ALSFRS-R 41.54±4.3 (22-47) and respiratory subscore 11.83±0.38 (11-12). MeanPhrenAmpl and SVC were weakly but significantly correlated at T0 and T1. At T1, MeanPhrenAmpl decayed 16.94±16.45% and SVC 13.5±16.86%. For the proposed drug effect, 174 and 272 patients would be needed to recruit using respectively meanPhrenAmpl and SVC decline as the primary outcome measurement (accepting no dropouts).

Discussion:
Contrary to SVC, meanPhrenAmpl is non-volitional and not associated with aerosolization risk. Lower recruitment number (98 patients less) would be needed, translating shorter inclusion period, trial length and costs, and probable lower missed data rate. MeanPhrenAmp is an alternative test in ALS clinical trials.

CLT-32: Reconsidering the revised amyotrophic lateral sclerosis functional rating scale for ALS clinical trials

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Objective:
To evaluate the impact of questionnaire revision on trial design, illustrated for the primary endpoint in ALS, the revised ALS functional rating scale (ALSFRS-R).

Methods:
We analyzed 21,497 measurements from 2,590 patients in the Pooled Resource Open-Access ALS Clinical Trial database that contains data from 23 clinical trials conducted since 1990. ALSFRS and ALSFRS-R total scores were calculated as the sum of items 1-10 and items 1-12; scores were divided by 10 and 12, respectively, to allow a direct comparison of the two questionnaires. Importantly, this linear transformation (i.e. dividing the total score by 10 or 12) does not impact the signal-to-noise ratio or the required sample size. For both the original and revised ALSFRS, we determined the signal-to-noise ratio and the required sample size to detect a 30% slowing of progression rate with 90% power for a 12-month clinical trial using linear mixed effects models. The signal-to-noise ratio and required sample size were used to compare the sensitivity of the ALSFRS and the ALSFRS-R for detecting treatment effects. Between-patient variability in monthly decline was defined as the standard deviation of the random slopes, whereas the signal-to-noise ratio was defined as the average monthly decline divided by the between-patient variability.

Results:
The average ALSFRS decline per item was faster compared to the ALSFRS-R (0.096 vs. 0.090 points per month), resulting in a better signal-to-noise ratio. Consequently, the sample size required is 270 patients when using the ALSFRS-R and 252 when using the ALSFRS (difference of 7.1%, 95%CI 5.3%-9.6%). For 6-month and 9-month follow-up durations, results were similar (sample size differences of 6.0% and 6.9%, respectively). Creating other total scores (i.e. ALSFRS + item 11 or ALSFRS + item 12), or selecting a more fast-progressing subgroup of patients (i.e. patients with a $\Delta FS > 0.50$ points per month), did not alter these results.
In other words, enrolling 200 patients would provide 79.6% power when using the ALSFRS-R versus 82.3% power when using the ALSFRS as primary endpoint. The diminished signal-to-noise ratio of the ALSFRS-R is mainly driven by the relatively slow rate of decline of item 11 (0.065 points per month) and item 12 (0.046 points per month) compared to item 10 (0.074 points per month). Although adding items 11 and 12 reduces the slope variability in total score, the slowing of average rate of decline is proportionally larger and, ultimately, results in a larger required sample size.

Conclusions:
The original ALSFRS can detect smaller treatment effects with identical sample sizes compared to the ALSFRS-R, thereby preferring the original over its revision. This relatively simple assessment could aid in selecting optimal endpoints for future clinical trials and maximize the likelihood of identifying effective treatments for ALS and other neurodegenerative diseases.

CLT-33: Superiority of the Updated Awaji criteria over The El Escorial revised Airlie House diagnostic criteria in JETALS (The Japanese Early-Stage Trial of High Dose Methylcobalamin for Amyotrophic Lateral Sclerosis)

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Background: The El Escorial revised Airlie House diagnostic criteria (rEEC) are widely accepted, but its low diagnostic sensitivity has been considered an issue. The updated Awaji criteria (UAC) adds the electrophysiological fasciculation potential to the rEEC as evidence of an active denervation. UAC revealed a higher sensitivity compared to rEEC. We conducted The Japanese Early Stage Trial of High Dose Methylcobalamin for Amyotrophic Lateral Sclerosis (JETALS) to confirm the efficacy and safety of methylcobalamin 50mg for ALS patients within 12 months after the onset (E0302-J081-763). We adopted the UAC for the first time in the world to our knowledge to enroll the early stage ALS patients with effectively.

Objectives: To compare the sensitivity of the UAC over the conventional rEEC in JETALS to recruit ALS patients within 12 months after the onset.

Methods: JETALS is a prospective, multicenter, placebo-controlled, double-blind, randomized phase III study conducted at 25 tertiary neurology centers. Patients diagnosed with ALS corresponding to the sufficient grades (definite, probable, or probable-laboratory supported) in the UAC within 12 months from onset were registered. At the registration, patients were evaluated by rEEC as well as UAC to compare the sensitivity of the two diagnostic criteria.

Results: From October 2017 to August 2019, 207 patients were registered. The median duration from onset to registration was 8.4 (3.1 to 11.5) months. One patient who met the probable grade in the UAC and rEEC was excluded because she determined not to have ALS by its clinical course and examination after registration. Twelve of 206 patients (6%) corresponded to the sufficient grades in the UAC, and didn't correspond in the rEEC.

Discussion and conclusions: The UAC has the superiority over rEEC in JETALS. Fasciculation potential is observed in the early phase of ALS, so that the UAC was reported to diagnose about 6 months earlier compared to the rEEC. Among 12 patients who didn't meet the sufficient grades in the rEEC, 3 patients met definite, 2 patients met probable, 7 patients met probable-laboratory supported grade in the UAC, respectively. The result that the patients with probable-laboratory supported grade had the majority may indicate that the UAC is especially useful for the patients with severity grade stage 1 (clinical symptom is restricted in one lesion). In conclusion, the UAC may contribute registration for early stage ALS patients.

CLT-34: Time is of the Essence: Communication with Potential Participants in a Motor Neuron Disease Trial Launch

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Background:
MND-SMART (Motor Neuron Disease Systematic Multi-Arm Randomised Adaptive Trial) is a multi-site UK trial seeking to address the lack of effective treatment options for people with MND. Patient public involvement (PPI) informed the design of MND-SMART and continues to be essential in delivering a patient-focused trial.

Methods:
We reviewed the email correspondence between potential participants, and their representatives, to the central trial mailbox between 15/01/2020 and 08/05/2020, following the public launch of the trial. Emails were categorised by sender, participation decision, initial contact or reply. We extracted key themes representing the content of the emails; seeking or providing information and including positive or negative content.

Results:
327 emails were included in the audit. A clear intent to participate was expressed in 62% of emails. 49% of emails were an initial contact with the trial team. 35% were sent by a potential participant, 36% by their carer/representative and 6% by a researcher or clinician, the sender could not be determined for the remaining emails. Frequently discussed themes included; seeking details on the trial intending to participate (28%), providing personal information (24%), expressing positive emotion about participating (18%) and lived experience of MND (12%).

Conclusions:
A direct line of communication with the coordinating trial team supports potential participants and their representatives in raising questions and feedback. Continuing PPI after a trial launch enables us to evaluate the clarity of information provided and address areas of concern amongst potential participants, with the ultimate goal of improving engagement and optimising trial recruitment.

Trial identifier: NCT04302870

CLT-35: The Impact of the Covid-19 Pandemic on the Administration of ALS Clinical Trials and their Outcome Measures at the Clinical Research Unit, Montreal Neurological Institute and Hospital

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Background:
Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease that due to loss of motor neurons progressively leads to death. There is no cure for this disease and only two disease modifying drugs are approved by the FDA. ALS research gained increased public attention in 2014 with the famous “ALS ice bucket challenge”. Donations allowed for the emergence of more fundamental research, increasing potential therapies. In 2017, ALS Canada's vision was to make ALS a treatable disease by 2024. The pharmaceutical pipeline includes up to 267 (Pharmaceutical Technology) diverse candidates across all developmental trial stages. Of these, 5% are in late-stage and have a strong chance at being commercialized. All of these taken together emphasize the fact that clinical trials for ALS are considered absolutely essential as they provide potential therapeutic treatment to patients (Wobst et al, 2020). On 11 March 2020, the WHO organization characterized the COVID-19 as a pandemic. This announcement urged massive lockdowns around the world and Quebec’s officials mandated the closure of all non-essential activities.
During this first wave of Covid-19 in March-May 2020, ALS clinical trials at the Clinical Research Unit (CRU) at the Montreal Neurological Institute and Hospital continued as essential services. Stricter measures were adopted in administering outcome measures for the safety of both the patients and the raters. Reliable outcome measures contribute to clinical trial results and consequently assist with drug development and marketing (Paganoni et al, 2014). The main concern of administering outcome measures during the pandemic was ensuring patient and rater safety, while also making a strong effort to administer the assessment in a consistent, valid and reliable manner. Trained personnel at the CRU had to make special considerations during the administration of assessments during this pandemic in order to ensure patient and rater safety, and maintain study integrity.

Objectives:
Implementation of new adapted measures for the administration of clinical trial and their outcome measures, including slow/forced vital capacity (S/FVC), hand-held dynamometry (HHD) and the ALSFRS-R, during the first wave of the Covid-19 pandemic will be analyzed.

Methods:
A retrospective internal review of ALS clinical trials run at the CRU between March 2020 and May 2020 will be conducted. The review will include tracking the number of outcome measures missed or incomplete due to Covid-19 related issues. As well, the CRU management and site raters (SVC, FVC, HHD and ALSFRS-R) will be consulted to discuss adaptations and/or considerations made to the administration of the assessments during the specific timeframe.

Results:
This is a work in progress. Results presented will highlight how many assessments were missed due to Covid-19 over time, as well as the main changes that raters had to implement to maximize safety. Common themes will be highlighted.