2322 RESULTS OF THE AUSTRALIAN RESCUE-ALS TRIAL: A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF CNM-AU8 TO SLOW DISEASE PROGRESSION IN ALS

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Objective The objective of RESCUE-ALS was to evaluate the efficacy and safety of CNM-Au8, a suspension of catalytic gold nanocrystals that enhance cellular energy metabolism, as a disease-modifying treatment for amyotrophic lateral sclerosis (ALS).

Methods Participants were randomized 1:1 (active:placebo). The primary endpoint was the percent change in the summated motor unit index (MUNIX) scores for four selected limb muscles after 36 weeks of treatment. Secondary/exploratory endpoints included respiratory function, ALS disease progression, and quality of life.

Results In total, 49 participants were screened and 45 enrolled (73% limb onset, 27% bulbar). In the CNM-Au8 30mg cohort, there was significant reduction of ALS disease progression (occurrence of death, tracheostomy, or need for non-invasive ventilatory support or gastrostomy tube placement; 37% absolute risk reduction, p=0.02), improved proportion free from > 6-point ALSFRS-R decline (49% vs. 8%; p=0.04, chi-square test), improved quality of life (LS mean difference: 0.9; 95% CI: 0.2 to 1.6; p=0.02). Additionally, there was a trend for improvement in the summated MUNIX score to week 36 (primary endpoint) that was more prominent in limb-onset ALS (LS mean difference: 20.9%, 95% CI: -2.2% to 44.0%, p=0.074), and a trend for improvement of respiratory dysfunction. CNM-Au8 was well-tolerated, and no safety signals were observed.

Conclusions CNM-Au8, in combination with riluzole, was safe and well-tolerated in ALS. CNM-Au8 may provide functional benefit by slowing ALS disease progression.

2344 THE 1H-MRS METABOLITE SIGNATURE OF CORTICAL HYPEREXCITABILITY IN ALS

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Cortical hyperexcitability is an established clinical feature present in the earliest stages of disease onset in ALS and can be used to detect subclinical upper motor neuron dysfunction. The abnormality is believed to reflect an underlying glutamate-induced excitotoxicity implicated in disease pathogenesis and linked to functional motor impairment. While a large body of TMS and MRS research have independently documented the disease signature of ALS, their association remains to be investigated.

Objectives Characterize the relationship between cortical motor hyperexcitability and metabolite abnormalities.

Examine asymmetry differences in hemispheric cortical motor integrity.

Methods 32 non-familial ALS patients and 17 age-education matched healthy controls were recruited. All participants received an MRI scan (3T GE MR750; 32-channel head coil) and single-voxel 1H-MRS (PRESS) data was sequentially acquired from the hand region of the left and right motor cortices. All patients underwent TMS to determine presence of cortical hyperexcitability based on SICI threshold (≤ 5.5).

Results As a whole, ALS patients demonstrated a consistent reduction in NAA/Cr in the left (p=0.02) and right (p=0.01) hand region, without evidence of hemispheric imbalance relative to controls. Patients with cortical hyperexcitability, however, demonstrated significantly higher levels of Glu/Cr and NAA/Cr across both hemispheres (p values < 0.05), relative to patients with a normal SICI. Interestingly, patients with a normal SICI demonstrated a significantly higher degree of hemispheric NAA/Cr imbalance (p=0.04).

Conclusions Cortical excitability is associated with a consistent pattern of metabolite abnormality across cortical hemispheres underlying hand motor function in ALS.

2424 HALLUCINATIONS IN NON-PARKINSON'S NEURODEGENERATIVE DISORDERS: COGNITIVE AND NEUROIMAGING EVIDENCE FOR A TRANS-DIAGNOSTIC ATTENTIONAL THEORY OF HALLUCINATION GENERATION

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Objective To determine the rate of hallucinations across non-Parkinson's neurodegenerative disorders including Frontotemporal Dementia and explore the underlying cognitive and neural basis for the development of these symptoms

Methods Patients were recruited (n=429) and assessed over a 10-year period at the FRONTIER FTD multidisciplinary research clinic. Patients were assessed at their first visit by means of a clinical interview, a battery of neuropsychological tests and MRI. Data was analysed according to 3 tiers; 1) rate of hallucinations across neurodegenerative disorders; 2) the relationship between neural structures, cognition, behaviour and hallucinations and 3) the impact of the *C9orf72* expansion on expression of hallucinations.

Results Tier 1: The majority of cases of hallucinations occurred in patients with bvFTD (22%), Alzheimer's disease (13%), LPA and Corticobasal syndrome (11%). Rate of hallucinations were low for posterior cortical atrophy (9%), Primary progressive aphasia (PPA) including left and right Semantic Dementia (SD; 6%), PPA-non-fluent variant and Progressive supranuclear palsy (0%; p<0.006). Tier 2: Attentional measures differed between groups (all p<0.02) with hallucinators making more frequent attentional and processing speed errors while structural changes affected regions of attentional networks centred on the prefrontal cortex (p<0.001). Tier 3: Attentional processes were also implicated in *C9orf72* carriers with hallucinations as well as visual