Welcome to the 2025 NMSG Study Group Meeting!

Richard J. Barohn MD
Chair, Neuromuscular Study Group

Michael G. Hanna, MD
Co-chair, Neuromuscular Study Group

Dear Colleagues,

On behalf of the Neuromuscular Study Group (NMSG), we are delighted to welcome you back to Stresa, Italy for our 26th Annual Scientific Meeting.

For nearly three decades, the NMSG has united researchers from around the world to collaborate on advancing neuromuscular science. This meeting in particular has become a unique opportunity for our community to come together for a vibrant exchange of ideas that reinforces our commitment to progressing innovation in our field. Whether you are presenting a poster or discussing trials between sessions, we encourage you to engage fully with your colleagues and our industry partners as your active participation will greatly strengthen the value of our time together. A few meeting highlights for this year:

- Young Investigators: We welcome back this valuable session where emerging talent can connect with and learn from established leaders in the field. Join us at 3:35pm on Friday.
- Abstract Posters Presentations: We had an unprecedented number of submissions this year with 163. Please stop by to see their work at 6pm on Friday in the Tiffany room.
- Industry Partners: We appreciate the immense industry involvement from Europe and the United States. Please join us for their presentations starting at 1:45pm on Saturday and visit their tables daily in the Gallè room.
- Neuromuscular Research 2-Year Fellowship Program: We are proud to continue our partnership with the American Brain Foundation to fund this program. Our current fellow Sophie Rengarajan, M.D., Ph.D., will present her research just before our keynote session on Saturday at 6pm.
- Shark Tank: In its seventh year, the Shark Tank session will feature four exciting proposals with the winner receiving a $10,000 grant. New this year: Everyone who attends the session will be able to score the presentations. Join us at 9:45am on Sunday.

Outside of the scientific program, take time to enjoy the beauty of Stresa. With its elegant promenade, historic villas, and the famed Borromean Islands just offshore, Stresa offers a truly inspiring setting. We hope you will soak in the scenery, savor Italian hospitality and cuisine, and make the most of this charming location during your visit.

We are excited for the continuing opportunity to share breakthroughs, clinical insights, and new ideas that can improve the treatment and care of our patients. Let us continue to embrace the spirit of collaboration as we explore the latest research and inspire one another with our findings.

Contents

2025 NMSG Scientific Meeting Platform Presentations

#1120 Side-by-side evaluation of systemic AAV8, 9 and rh74 transduction in human muscle

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Introduction: Adeno-associated virus (AAV) 8, 9, and rh74 are currently used in multiple clinical trials to treat inherited neuromuscular diseases. However, their performance has never been compared in human muscle.
Objectives: This study aims to compare the transduction profile of AAV8, 9, and rh74 in human muscles.
Methods: To evaluate systemic AAV transduction in human muscle, we developed a human muscle xenograft model. We then delivered AAV8, 9, and rh74 to human muscle by tail vein injection at 5E+12 vg/kg. One month after the AAV injection, we quantified AAV vector genome copy number, transcript copy number, and the percentage of AAV-expressing myofibers in human muscle.
Results: The grafted human muscle underwent degeneration and necrosis in the first month and then regenerated. Human muscle was fully regenerated by the fourth month and expressed both type I and type II myofibers. The vector genome copy number for AAV8, 9, and rh74 was 1.57 ± 2.02, 2.64 ± 2.55, and 2.43 ± 2.23 vg/diploid human genome, respectively. The AAV transcript copy number for AAV8, 9, and rh74 was 110.23 ± 185.26, 775.06 ± 1,053.34, and 136.74 ± 115.99 transcripts/ng of human cDNA, respectively. The percentage of AAV-expressing myofibers was 4.82 ± 3.40%, 26.60 ± 16.32%, and 8.25 ± 8.77%, respectively. AAV9 was significantly different from AAV8 and rh74. No statistically significant difference was detected between AAV8 and rh74.
Conclusions: We established a platform to study systemic AAV transduction in human muscle. We showed that AAV9 significantly outperformed AAV8 and rh74 following intravenous injection.

#1188 The Role of Epigenetic Regulation of DMPK in Congenital Myotonic Dystrophy

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Introduction/Objectives: Congenital myotonic dystrophy (CDM) is the most severe form of myotonic dystrophy type 1 (DM1). DNA methylation changes at the DMPK locus are present in CDM, but the specific role these epigenetic modifications play in CDM pathogenesis remains unclear.
Methods: DNA methylation at the DMPK locus was evaluated in skeletal muscle biopsies and matched blood samples from 60 CDM patients, 30 adult DM1 patients, and 20 age-matched controls. Methyl-CpG binding domain sequencing (MBD-Seq) assessed global methylation patterns in these samples. Methylation changes were compared to changes in RNA splicing as well as long term outcomes in the CDM cohort.
Results: Differing methylation patterns throughout specific regions of the DMPK locus, such as CpG island 43, are apparent when comparing muscle and blood samples from the same individuals. Results from methylation sequencing of the DMPK locus also demonstrates the utility of sampling across a range of developmental ages – our newborn and infant samples show 100% hypermethylation at the CTCF1 site (consistent with previously studies) but our adolescent CDM samples show hypomethylation patterns at the CTCF1 site, consistent with patterns from adult DM1 samples. These findings suggest that methylation changes in key regulatory regions of DMPK may correlate with disease progression.
Conclusions: This study provides the first comprehensive analysis of developmental methylation patterns at the DMPK locus in CDM patients, revealing dynamic changes that correlate with disease progression. Our findings suggest epigenetic modifications at the DMPK locus play a critical role in CDM pathophysiology. Identification and characterization of disease modifying factors, such as methylation changes, will provide a foundation for future therapeutic development for CDM, the most-severely affected DM patient population.

#1247 100 Adults with Spinal Muscular Atrophy at the Dawn of Treatment: A Bone Health Focus

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Introduction: As disease-modifying treatments for spinal muscular atrophy (SMA) are implemented, co-morbidities in adults including osteo-pathologies are increasingly recognised. Guidance for managing such issues is incomplete. We present data on bone health from, to our knowledge, the UK's largest single-centre adult SMA cohort.
Objectives: We aimed to quantify the following bone heath specific parameters in our cohort:
1. Fracture incidence and type
2. Implementation of bone density scanning
3. Cholecalciferol status and supplementation
Methods: Data was prospectively recorded for 100 patients (51% male; 49% female, average age 32), at the National Hospital for Neurology and Neurosurgery from 2022-2025.
Results: SMA subtypes were SMA3 (55%), SMA2 (44%) and SMA1 (1%). Where available ethnicities were: White (n=57), Asian (n=13), Black (n=4), Mixed (n=2) and Other (n=4). Fracture incidence was 23%, of which 82% affected the lower limb(s). Most fractures (78%) occurred in SMA3 patients who have been ambulant. However, 55% of these patients have since lost the ability to ambulate. Bone density scans were recorded in 39% of patients who had fractures (89% of scans occurred post fracture). Bone density scans were recorded in 11.7% of non-fracture patients. Of the overall cohort, 39% were vitamin D deficient/insufficient, and 60% prescribed cholecalciferol.
Conclusions:_The high fracture rate is particularly pertinent, given that lower limb fractures can accelerate ambulation loss in SMA3 patients. Consistency in bone-density scanning is lacking and generally reactive to fracture occurrence. Overall, this highlights the importance of bone health considerations in SMA patients.

#1264 Nutritional and Swallowing Assessment in Patients with Myotonic Dystrophy Type 1: A Cross-Sectional Study

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Introduction: Myotonic dystrophy type 1 (DM1) is a multisystemic genetic disorder characterized by muscle weakness, myotonia, and progressive involvement of respiratory, metabolic, and gastrointestinal systems. Dysphagia and malnutrition are common but often under-recognized features.
Objectives: This study aimed to evaluate the nutritional status, feeding characteristics, and swallowing difficulties in a cohort of patients with DM1, to better understand their clinical needs and guide multidisciplinary management.
Methods: We analyzed data from 47 patients with genetically confirmed DM1. Parameters included BMI, the Malnutrition Universal Screening Tool (MUST), the Eating Assessment Tool (EAT-10), need for mealtime assistance, food consistency modifications, cough reflex during meals, and deambulation.
Results: The cohort had a mean age of 43.2 years and was 57% female. Malnutrition risk was identified in 17% of patients (MUST ≥ 2), with 10 individuals classified as underweight (BMI < 18.5). Swallowing difficulties were prevalent: 34% had an abnormal cough reflex during meals and 34% scored ≥3 on EAT-10, suggesting dysphagia. Only 6 patients required assistance during meals. Despite these findings, most patients consumed normal-texture foods, and only 3 required modifications. All patients maintained independent ambulation.
Conclusions: Patients with DM1 frequently present with subtle signs of dysphagia and malnutrition, despite preserved ambulation and minimal visible feeding impairments. Routine screening with tools like EAT-10 and MUST is essential to identify at-risk individuals and initiate timely dietary and rehabilitative interventions.

#1274 Uncovering Brain Structure and Cognitive Dysfunction in Myotonic Dystrophy Type 2

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Introduction/Objectives: Nearly 70% of myotonic dystrophy type 2 (DM2) patients report cognitive symptoms as a major source of disability. Limited brain imaging studies suggest cerebral white matter (WM) is primarily affected in DM2; however, the mechanisms underlying cognitive dysfunction remain poorly understood.

Methods: 3T brain MRIs were acquired from 38 adults with DM2 and 24 age-and sex-matched healthy controls (HC). Brain morphometry and WM integrity were assessed using T1-MPRAGE and DTI. DTI metrics (fractional anisotropy [FA], radial, axial, mean diffusivity [RD, AD, MD]) and gray matter (GM) volumes were compared between groups. Comprehensive cognitive measures and plasma biomarkers were evaluated and correlated with imaging findings.

Results: Among 62 participants (55% female), age (DM2=57.5 vs. HC=60.2 years) and education (DM2=16.2 vs. HC=17.0 years) showed no difference. Compared to HC, widespread WM integrity disruptions (lower FA, higher RD) were the most prominent abnormality in DM2 (mean differences: FA=0.035; P-val<0.0001 and RD=0.00005; P-val<0.0001), suggesting WM microstructural pathology. Cortical GM loss was observed across multiple lobes (t-value=4.46; P-val<0.0001). DM2 participants showed significant deficits in executive function (p<0.003) and episodic memory (p<0.017). We found strong correlation between superior frontal FA vs. executive function (r=0.44, P-val=0.008); superior frontal/parietal GM volume vs. working memory (r=-0.41, P-val=0.015). Plasma biomarkers showed significant elevation in P-tau181 (log_{FC}=1.03, P-val_{FDR}=0.006), P-tau231(log_{FC}=0.8, P-val_{FDR}=0.016), total-tau (log_{FC}=0.56, P-val_{FDR}=0.03), and NfL (log_{FC}=0.63, P-val_{FDR}=0.02).

Conclusions: Findings support strong associations between measures of DTI and GM volume and cognitive dysfunction in DM2. Elevated plasma markers further indicate brain involvement. Longitudinal studies are required to elucidate disease mechanisms.

I. Clinical Research and Patient Management

#1283 A Bayesian Network Meta-Analysis of the Efficacy and Safety of Chronic Inflammatory Demyelinating Polyneuropathy Treatments across 9 Placebo-Controlled Trials

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Introduction: Recent advances are changing the therapeutics landscape for chronic inflammatory demyelinating polyneuropathy (CIDP). After decades of traditional therapies with intravenous immunoglobulin (IVIg) or plasmapheresis, a new therapy was recently approved, and other targeted therapies are being tested in clinical trials.

Objectives: As these novel treatments progress in development, there is an unmet need for comparisons of their demonstrated efficacy and safety to delineate the future treatment paradigm.

Methods: We conducted a Bayesian network meta-analysis to compare the efficacy and safety and ranked treatments using Surface Under the Cumulative Ranking (SUCRA). We searched MEDLINE, Embase, and three other databases for double-blind randomized, placebo-controlled trials in CIDP reporting efficacy as change in Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Score, Rasch-built Overall Disability Scale (RODS), Medical Research Council (MRC) sum score, dominant hand grip strength (kPa), or number of relapsing patients. We identified 9 trials (n=964) reporting these outcomes. The main therapies represented were immunoglobulin therapies, methotrexate, fingolimod, FcRn inhibitors (efgartigimod, rozanolixizumab), and anti-CD20 therapy (rituximab).

Results: For the efficacy outcomes, INCAT, RODS, MRC, and dominant hand grip strength, there were only modest benefits, and SUCRA score rankings suggested highest relative efficacy ranking of FcRn inhibitors and B cell depletion. Fingolimod had the highest probability of having the most adverse events.

Conclusions: This meta-analysis compares novel therapies and further analysis incorporating other new therapies is ongoing.

#1280 Efficacy and Safety of Onasemnogene Abeparvovec Gene Therapy in Children With Spinal Muscle Atrophy: a Single-Center Experience

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Introduction: Spinal muscular atrophy (SMA) is a genetic neuromuscular disorder with progressive loss of motor neurons resulting in muscle weakness and loss of movement. It is caused by a mutation in the SMN1 gene, important for the survival of motor neurons. Gene therapy with onasemnogene abeparvovec (OA) significantly improved the prognosis of SMA in children.

Objectives: This study evaluated efficacy and safety of OA in children with SMA.

Methods: The retrospective study assessed twelve children with SMA, treated with OA between 24 days and 5 months of age (two cases of nusinersen bridge therapy). CHOP – INTEND scale scores, WHO gross motor milestones, need of nutritional/ respiratory support and adverse effects were collected and statistically analysed.

Results: CHOP- INTEND scale scores were improved in 100% of the study group. Milestones: head control was achieved in 100% of the study group. 58% of the participants, older than 1,5 years reached walking independently. None of them needed nutritional nor respiratory support. Mild thrombocytopenia and hypertransaminasemia were observed. No severe adverse effects were reported except of Influenza coinfection case with transaminasemia -30xULN.

Conclusions: This first study from the South of Poland underscores efficacy and safety of gene therapy with onasemnogene abeparvovec.

#1277 Comparative Evaluation of Respiratory Assessments in Inclusion Body Myositis from INSPIRE-IBM Study

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Introduction: A huge unmet need in sporadic Inclusion Body Myositis (IBM) research is the lack of long-term prospective longitudinal data on disease behavior and progression and the influence of the various blood biomarkers (NT5c1A antibodies and highly differentiated T lymphocytes) on disease behavior and progression.

Objectives: Previous studies in small IBM cohorts have shown that seropositivity for NT5c1A antibodies is associated with significantly reduced pulmonary function, particularly in maximum inspiratory pressure (MIP) and forced vital capacity (FVC), suggesting more severe respiratory involvement. However, larger-scale studies are needed to confirm this relationship.

Methods: A 13-center observational prospective study is ongoing involving 150 patients with IBM (INSPIRE-IBM). Each subject will be seen every 6 months (5 times points) over a 2-year period, and will have serial collection of disease related data, including physical exams, functional and respiratory assessments.

Results: As of January 2024, the study has successfully enrolled 150 patients. By February 2025, 50 participants remain active, 38 have withdrawn early, and 62 have completed the study. Additionally, 24 biopsies have been collected to date. We analyzed pulmonary function data collected at baseline, 12 months, and 18 months, including sitting and supine FVC, MIP, and maximum expiratory pressure (MEP) to examine correlations with NT5c1A seropositivity.

Conclusions: Data analysis is currently underway and will be presented at the upcoming conference. Based on earlier findings, we anticipate that NT5c1A-seropositive participants will again demonstrate lower pulmonary function test results, providing greater evidence of respiratory involvement in this subgroup.

#1273 IMPROVING WOMEN HEALTH IN NEUROMUSCULAR DISEASES

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Introduction: Women health is often an underestimated issue for patients with disability. Emotional education and sexuality are themes that have a great impact on QoL. New molecular therapies can change NMDs' natural history and motherhood became a possibility for affected women, hence contraception and family planning are crucial.

Objectives: To create a pathway of care for women with NMDs through the collaboration between neurologists and gynecologists, based on patient's needs.

Methods: we conducted an online survey on 450 NMD women in charge to our centre to focus on their needs and analyze challenges experienced during gynecological consultations. We discussed with gynecologists the clinical risks and main problems for NMD women and defined a follow-up plan.

Results: By now we analized 182 questionnaires (ongoing). SMA patients were more active in filling the survey, followed by FSHD/congenital myopathies, and last DM1/DM2. Mobility barriers, lack of knowledge about NMDs specific issues and waiting lists were the main obstacles, hindering both family planning and preventive screening tests with potential delay in detecting cancer. Based on these findings, literature and our experience, we delineated a multidisciplinary pathway of care for NMD women based on age and disease specific highlights.

Conclusions: Multidisciplinary approach to women health is mandatory in NMDs to reach a high level of QoL besides disability. A barrier-free gynecological outpatient clinic in every neuromuscular specialised centre could improve adherence to preventive screening tests. A shared pathway of care could be a valuable instrument to assure NMD women adequate access to specific health services.

#1269 Sleepy Patients with Myotonic Dystrophy Type 1 show no specific neuropsychological or neuroimaging differences compared to non-Sleepy patients

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Introduction: Excessive daytime sleepiness (EDS) is a common and burdensome symptom in myotonic dystrophy type 1 (DM1). While CNS involvement is widely accepted, it remains unclear whether EDS in DM1 is associated with specific white matter hyperintensity (WMH) patterns or neuropsychological features.

Objectives: This study aims to explore whether functional brain changes or cognitive profiles can help identify DM1 patients with EDS.

Methods: Genetically confirmed ambulant adult DM1 patients underwent neuromotor, respiratory, and neuropsychological evaluations. EDS was assessed using the Epworth Sleepiness Scale (ESS), with ESS >10 indicating sleepiness. Brain MRI was analyzed using the Fazekas index and automated WMH quantification (QuantibND software).

Results: Twenty-one ambulant DM1 patients (mean age 42.2 ± 11.4 years) with stable respiratory function were recruited; 6 had EDS. Sleepy patients were younger (mean age 37.2 ± 11.6 vs 47 years). No differences were detected in neuropsicological assessment (CWST,TM test,POMS). No significant differences in WMH were observed between sleepy and non-sleepy groups:

- Fazekas index: 0.83 ± 1.17 vs 1.13 ± 1.73
- WMH count: 26.5 ± 28.1 vs 28.6 ± 28.3
- WMH volume: 0.69 ml ± 1.22 vs 0.69 ml ± 0.99
- WMH relative volume: 0.05% ± 0.12 vs 0.06% ± 0.11

Conclusions: EDS affects 20–30% of DM1 adults. Preliminary findings show no distinct neuroimaging or neuropsychological features in sleepy patients, despite their younger age. Ongoing analysis, including CSF data and volumetric brain MRI may provide further insights into sleep–wake disturbances in DM1.

#1268 Beyond neurology-center care in the outpatient neurology clinics: early multidisciplinary care improves adherence and patient alliance

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Introduction: The context of outpatient visits in a Neurology Clinic may not allow to go beyond neurology diagnosis and pharmacological treatment and follow-up and care are usually planned in follow-up visits as available.

Objectives: The aim is to present the results of an early care plan during first-time visits at the NeMO site, a dedicated neuromuscular multidisciplinary clinic to emphasize the importance of early multidisciplinary management in neuromuscular disorders.

Methods: Retrospective qualitative analysis of needs, aids and homecare services detected by the Nurse Coach Service in the outpatient clinic at the NeMO site are presented from January 2024 to June 2025.

Results: 100 patients with ALS and muscular dystrophies took part in an early Nurse Coach outpatient care plan. The main themes reported were: (i) clinical nursing problems (69%) like pain, constipation, swallowing difficulties; (ii) psychological needs (61%); (iii) economic aspects (55.8%) (disability rights, aids..) (iv) educational needs (43%) (diagnosis, family planning); (v) social needs (35%).

Conclusions: The family context and the economical status must be taken into consideration as early as possible; elements beyond neurology-centered care can affect the disease course and therapeutic adherence. An early multidisciplinary management is recommended.

#1266 Exploring treatment expectations in neuromuscular disorders using the Goal Attainment Scale

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Introduction: Patient-Reported Outcomes (PROs), which reflect the patient's perspective on meaningful changes in daily function, have become an important complement to objective neuromotor assessments, particularly given the wide phenotypic variability observed in neuromuscular diseases.

Objectives: This study investigates the use of the Goal Attainment Scale (GAS) in patients with Spinal Muscular Atrophy (SMA), Facioscapular Muscular Dystrophy (FSHD), and Myotonic Dystrophy (DM1) to approach patient expectations and explore whether their self-defined goals were or were not captured by items in the existing scales.

Methods: 58 SMA, 15 FSHD, and 30 DM1 patients referred to the NeMO Clinical Centre (Milan) were enrolled. The GAS scale was administered at baseline and a follow-up visit. Goals were clustered into macro-domains and correlated to the corresponding objective neuromotor existing scales for each disease.

Results: Data from 58 SMA patients demonstrated the reliability and validity of GAS. 149 SMART goals were grouped into 15 macro-domains, with mobility, upper limb strength, and ADL being the most frequent. 72% of goals were mapped to standardized scales. Unmet goals involved ADL, endurance, and upper limb function. Analysis on FSHD and DM1 is ongoing.

Conclusions: In SMA, GAS appears to offer an individualized, quantifiable measure of goal attainment, supporting realistic treatment planning, as most SMART goals are captured by existing tools. Ongoing analysis will determine its usefulness in FSHD and DM1 and may support its broader adoption across neuromuscular disorders to guide treatment goals and define clinically meaningful outcomes.

#1265 Longitudinal Psychometric Properties of the FSHD-HI in a large multicentric cohort of people living with Facioscapulohumeral Muscular Dystrophy (FSHD)

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Introduction: Patient-reported outcomes, like the FSHD Health Index (FSHD-HI), are increasingly important to provide clinical meaningfulness to potential clinical changes which are expected in this new therapeutic era. Validity and reliability of the FSHD-HI have been reported across countries but data on sensitivity to change and responsiveness need further investigation.

Objectives: To evaluate sensitivity to change and estimate minimal detectable change (MDC95) of FSHD-HI over 24 months.

Methods: Patients with genetically confirmed FSHD were enrolled as part of an observational longitudinal study within the ReSolve group and the FSHD-HI was used. The 95% confidence Minimal Detectable Change (MDC_{95}) was estimated using distribution-based method, considering SEM (Standardized Error of Measurement) approach. Sensitivity to change was assessed through change score analysis.-

Results: Preliminary data from a cohort of 150 FSHD patients were longitudinally assessed at baseline and after a 24 months follow-up period. MDC_{95} value for total score was ± 19.37 points whereas MDC values for the subscales ranged from ± 5.20 (gastrointestinal issues) to ± 28.65 points (core strength function). Globally, no significant median change was observed over time.

Conclusions: These preliminary data suggest that over a 24-month time frame, the FSHD-HI reflects the stability of the functional scales. Additional analysis (calculation of the MCID using the domain delta as an anchor; responsiveness by comparing clinical outcome changes between groups analyses) in a larger sample of patients are currently ongoing to explore whether there are specific domains which actually change over time and are captured by the FSHD-HI.

#1261 Natural History of Facioscapulohumeral Muscular Dystrophy in the Indian Population: A 10-Year Longitudinal Study

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Introduction: Facioscapulohumeral muscular dystrophy (FSHD) is a progressive, inherited muscle disorder characterized by asymmetric muscle weakness and functional disability. Most FSHD studies focus on Western populations, with very limited data available on the South Asian population where more than 1/5th of world population resides. Our group recently published the first genetic data on Indian FSHD patients and established a cohort of over 200 genetically confirmed cases.

Objectives: Primary objective is to assess disease progression using clinical and imaging outcome measures. Secondary objectives include exploring the influence of D4Z4 methylation on disease severity and establishing a biobank for future research.

Methods: This 10-year study will enroll 300 genetically confirmed Indian patients, with annual follow-ups at AIIMS CNMD Clinic. Assessments include muscle strength (MRC grading, quantitative tests), functional performance (Motor Function Measure, 6-minute walk, FSHD Composite Outcome Measure), disease severity (FSHD Clinical Severity and Ricci scores), respiratory function (spirometry), and muscle MRI. Patient-reported outcomes included nutrition (MIND Diet), quality of life (SF-36), disability (FSHD-RODS), health index (FSHD-HI), and sleep (PSQI). Biospecimens (DNA and serum) will be collected and stored for future studies. Data will be managed in REDCap and analyzed with linear mixed-effects models.

Results: Imaging parameters and D4Z4 methylation levels are anticipated to show significant associations with functional decline and patient reported outcomes.

Conclusions: We will provide the first natural history of FSHD in the Indian population which will help to plan and recruit FSHD patients from India in global clinical trials. Biobank of yearly FSHD samples will help in future research especially on biomarkers.

#1260 Unraveling the Trajectory of LGMDR1 to Inform Clinical Trial Design

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Introduction: Calpainopathy (LGMDR1) is caused by loss-of-function mutations in the CAPN3 gene, which encodes calpain-3, a structural protein essential for muscle function. The disease leads to progressive muscle weakness and wasting, often resulting in loss of ambulation and reduced ability to work. LGMDR1 is among the most prevalent forms of limb-girdle muscular dystrophy (LGMD) worldwide. Despite its frequency, no approved therapies currently exist, though the condition is a strong candidate for gene replacement strategies. However, the genetic heterogeneity and slow progression of LGMDR1 have hindered the identification of reliable primary and secondary endpoints for clinical trials. Predictive tools that estimate individual disease trajectories could support the evaluation of therapeutic efficacy.

Objectives: To develop a predictive algorithm for LGMDR1 disease progression using a multilayer analysis of clinical, imaging, and biochemical data.

Methods: The CALNATHIS study is a monocentric, prospective trial enrolling 25 ambulant LGMDR1 patients. Over a 24-month period, we are collecting clinical, functional, muscle MRI, and biochemical data to identify biomarkers of disease progression and establish a predictive pipeline.

Results: Twelve-month interim data suggest relative stability in segmental muscle strength but a significant decline in walking performance. Muscle strength quantification data are currently undergoing statistical analysis and will be further consolidated to inform the development of the predictive algorithm.

Conclusions: This study aims to generate an algorithm capable of predicting disease severity up to two years following a clinical assessment, thereby enabling personalized disease monitoring and optimizing endpoint selection for future therapeutic trials.

#1257 Repeated Bout Effect is present in Muscle Diseases

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Introduction: The repeated bout effect (RBE) is mechanism where a single bout of unaccustomed eccentric exercise protects against muscle damage from subsequent bouts. Though the effect is well described in healthy, it has never been studied in patients with myopathies. In healthy, the RBE is only described using eccentric exercise, but unlike healthy persons, patients with myopathies can experience significant muscle damage with concentric exercise. This raises the question if patients with myopathies could also show RBE when performing concentric exercise.

Objectives: We are using an established concentric exercise intervention, shown to induce muscle damage in specific myopathies to characterize the RBE in these groups.

Methods: Patients with either Limb-Girdle Muscular Dystrophy R9 (FKRP), Becker Muscular Dystrophy and McArdle disease underwent two exercise bouts consisting of a high-intensity interval cycling exercise followed by a strength training test with one month in-between. Blood was collected at rest and 0-, 2-, 4- and 24-hours post-exercise for measurement of Creatine Kinase (CK).

Results: Results from the first 19 participants show a lower rise in CK ($p = 0.02$) after the second bout of exercise.

Conclusions: Our results shown the presence of RBE in these myopathies. More participants are planned to properly power the trial, and to explore if this mechanism differs between the diseases. As the mechanisms for disease varies among myopathies, it is likely that some patients might experience RBE in a similar fashion to healthy, while others may not. Results from this trial will be important when planning trials involving both exercise and biomarker outcomes

#1256 A Retrospective Case Series of Young IBM Patients

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Introduction: The classic presentation of inclusion body myositis (IBM) includes weakness of deep finger flexors (FF) and/or knee extensors (KE) with age >=45 years at symptom onset. There is increasing recognition of the fact that IBM can affect younger individuals.

Objectives: Characterize the clinical features of young onset IBM.

Methods: From July 2023 to May 2025 there were 69 patients seen by neuromuscular providers at the University of Colorado with a diagnosis of IBM. 7 cases with muscle biopsy at age <= 50 years were identified.

Results: An alternative diagnosis was confirmed in two patients; one had pathogenic VCP mutation and onset in late 40s, and the other had a pathogenic MYH2 mutation and onset in 30s. Two of the patients were male, had onset in their late 40s, and had positive anti-cN1a antibodies. Of these, one had proximal limb weakness and ankle weakness at onset. The other had proximal weakness with lesser FF and KE weakness at onset. Another patient was female, had onset in late 40s, had comorbid interstitial lung disease with positive Sjögren's antibodies, and had negative anti-cN1a antibodies. Symptoms started with proximal limb weakness and there was initial improvement on immunosuppression. After ~1.5 years, weakness stopped responding to treatment and progressed to significant FF and KE involvement. The last patient was female, had symptom onset in early 40s, positive anti-cN1a antibodies, prominent facial and axial weakness, proximal extremity weakness, finger extension and mild FF weakness. She was diagnosed with T-cell large granular lymphocytic leukemia. One patient was excluded because muscle biopsy was unavailable.

Conclusions: Patients initially diagnosed with IBM at age <=50 years often have an atypical pattern of weakness and are frequently found to have an alternative diagnosis on further investigations.

#1243 EXPLORING ACCURACY AND UTILITY OF ARTIFICIAL INTELLIGENCE IN THE REAL-WORLD MANAGEMENT OF MYASTHENIA GRAVIS

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Introduction: Myasthenia gravis (MG) diagnostic and therapeutic decisions are becoming increasingly complex due to scientific advancements, including six new FDA-approved therapies since 2021 and at least seven novel therapeutic classes under investigation. Timely, evidence-based management is critical to provide optimal care. Given increasing clinical demands and limited specialist access, artificial intelligence (AI) platforms may serve as valuable tools for real-time clinical decision support prior to reaching subspecialist care. This study evaluates whether AI can assist clinicians in navigating MG-related clinical scenarios through structured queries posed to three AI tools.

Objectives: To assess the accuracy, comprehensiveness, consistency, and clinical utility of AI-generated guidance in MG care.

Methods: We examined the performance of three large language models (LLMs), ChatGPT-4o, Gemini 2.5 Flash, and OpenEvidence, in extracting key diagnostic and treatment information on MG from current scientific literature. Five physician-designed query sets were used, each beginning with a general prompt followed by 2–3 prompts with more strict boundaries. Responses were compared across platforms and against expert answers.

Results: Despite providing similar answers, there were differences in the sources selected by each AI tool, with Gemini weighing scholarly sources similarly to less rigorous ones. Stricter query constraints did not consistently improve responses. Inaccuracies in cited references were also observed for Chat GPT. A detailed comparative analysis with scoring metrics will be presented.

Conclusions: There is an opportunity for AI generated guidance to improve care for MG patients. This study will provide initial comparative analysis among three commonly employed AI tools.

#1238 Skeletal muscle oxygen uptake impairments during functional activities in ambulatory spinal muscular atrophy (SMA)

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Introduction: Despite the availability of disease modifying therapies, muscle weakness, reduced endurance, and fatigue persist and impact people with SMA. While reduced SMN protein predominantly affects motor neurons, it also manifests as mitochondrial impairment. Previous work demonstrated reduced muscle oxygen uptake during maximal exercise; however, the impact of mitochondrial impairment has not been studied during functional tasks.

Objectives: Estimate muscle oxygen uptake during functional tasks and explore relationships with strength and function in ambulatory SMA.

Methods: Twenty individuals with SMA (19.7; 8.1-33.8 years) performed the six-minute walk test (6MWT) and ten-meter walk/run (10MWR). Fatigability was expressed as percent change of distance walked during the first and sixth minutes. Handheld dynamometry measured plantarflexor strength (HHD-PF). Near-infrared spectroscopy measured change in medial gastrocnemius deoxygenated hemoglobin (ΔHHbMG) during the 6MWT and 10MWR. Pearson correlation coefficients and mixed-model ANOVA examined associations and change in muscle oxygen uptake.

Results: $\Delta HhbMG_{6MWT}$ correlated with 6MWT (r=0.565; p=0.009) and 10MWR (r=-0.483; p=0.031) but not strength or fatigability(p>.05). $\Delta HhbMG_{10MWR}$ correlated with 10MWR time (r=-0.456; p=0.043) and $\Delta HhbMG_{6MWT}$ (r=0.526; p=0.017). Overall, the mean change in $\Delta HhbMG_{6MWT}$ across the 6MWT was not significant (B= .093; p=.732; CI = -.469 –.656). However, significant differences were observed in average $\Delta HhbMG_{6MWT}$ between minutes 1vs.2 and 1vs.3 (p< 0.001), and 1vs.4 (p=0.02).

Conclusions: Muscle oxygen uptake is associated with reduced endurance and gait speed in SMA. Moreover, achievement of steady state muscle oxygenation was prolonged. Therapeutics should target muscle mitochondria to rescue symptomatic patients and mitigate their residual disease burden.

Acknowledgments: This study is supported by an Investigator Initiated Grant from Genentech (ML- 44201)

#1231 100 Adults with Spinal Muscular Atrophy at the Dawn of Treatment: A Bone Health Focus

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Introduction: As disease-modifying treatments for spinal muscular atrophy (SMA) are implemented, co-morbidities in adults including osteo-pathologies are increasingly recognised. Guidance for managing such issues is incomplete. We present data on bone health from, to our knowledge, the UK's largest single-centre adult SMA cohort.

Objectives: We aimed to quantify the following bone heath specific parameters in our cohort:
1. Fracture incidence and type
2. Implementation of bone density scanning
3. Cholecalciferol status and supplementation

Methods: Data was prospectively recorded for 100 patients (51% male; 49% female, average age 32), at the National Hospital for Neurology and Neurosurgery from 2022-2025.

Results: SMA subtypes were SMA3 (55%), SMA2 (44%) and SMA1 (1%). Where available ethnicities were: White (n=57), Asian (n=13), Black (n=4), Mixed (n=2) and Other (n=4). Fracture incidence was 23%, of which 82% affected the lower limb(s). Most fractures (78%) occurred in SMA3 patients who have been ambulant. However, 55% of these patients have since lost the ability to ambulate. Bone density scans were recorded in 39% of patients who had fractures (89% of scans occurred post fracture). Bone density scans were recorded in 11.7% of non-fracture patients. Of the overall cohort, 39% were vitamin D deficient/insufficient, and 60% prescribed cholecalciferol.

Conclusions: The high fracture rate is particularly pertinent, given that lower limb fractures can accelerate ambulation loss in SMA3 patients. Consistency in bone-density scanning is lacking and generally reactive to fracture occurrence. Overall, this highlights the importance of bone health considerations in SMA patients.

#1229 Impact of Respiratory Impairment on Cognitive Performance in Myotonic Dystrophy Type 1: A Cross-Sectional Study

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Introduction: Myotonic Dystrophy type 1 (DM1) is characterized by multisystem involvement, including respiratory and cognitive impairment. The potential influence of respiratory impairment on cognitive performance remains underexplored.

Objectives: To investigate the relationship between respiratory function and cognitive performance in adults with non-congenital DM1.

Methods: We conducted a monocentric, retrospective, cross-sectional study including 43 consecutive DM1 patients (19 males; mean age 43 ± 12 years) referred to a tertiary care Neuromuscular Center (January-June 2024). Neuropsychological assessment included global cognition (MoCA), attention (digit span forward, TMT-A), working memory (digit span backward, TMT-B), executive functions (Stroop, TMT B–A, phonemic fluency), visuoconstructive and strategic abilities (ROCF), reasoning (SPM), semantic fluency. Respiratory assessment included spirometry (FVC %) and nocturnal cardiorespiratory monitoring (mean SpO_2, T90%, ODI). Group comparisons were performed using Mann–Whitney U-tests; correlations (Spearman ρ) and stepwise linear regressions were used to assess associations.

Results: Cognitive impairment (≥1 abnormal test) was present in 86% of patients. Lower FVC and T90 correlated with pathological TMT-A/B, Stroop times, phonemic fluency and ROCF. Mean SpO_2 correlated with TMT-A. In regression models adjusted for age and education, FVC was the best predictor of Stroop time and ROCF performance.

Conclusions: Respiratory dysfunction, particularly reduced FVC, is associated with specific cognitive deficits in DM1. These findings highlight the need for integrated respiratory and cognitive monitoring and suggest that optimization of respiratory function could have a potential role in cognitive disorders.

#1205 Inflammatory Polyradiculoneuropathy: Insights from Autoimmunity Secondary to Porcine Neural Tissue Exposure

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Introduction: In 2007, Mayo Clinic (Rochester, MN) reported a peculiar neurological disorder consistent with an inflammatory polyradiculoneuropathy (IPN) in employees at a swine abattoir in Minnesota.

Objectives: This study aimed to identify disease specific serological biomarkers of IPN.

Methods: Sera of 20 occupational IPN (OIPN) cases were evaluated for putative autoantigens using phage immunoprecipitation-sequencing (PhIP-Seq). Healthy and diseased controls, and other inflammatory neuropathies were evaluated using enzyme-linked-immunosorbent-assay (ELISA) and cell-based assay (CBA) for putative autoantigen.

Results: PhIP-Seq data identified synaptophysin and growth-associated protein 43 (GAP43) as dominant autoantigens. Synaptophysin- and GAP43-IgG were confirmed by ELISA and CBA in 15 and 12 OIPN cases, respectively. All healthy and diseased controls were negative for synaptophysin-IgG. Among the inflammatory neuropathies, 12 IPN cases were synaptophysin-IgG-positive, and one GAP43-IgG-positive. Clinical characteristics between OIPN patients who were dual antibody positive versus synaptophysin-IgG only positive were similar. Thirteen of 15 (87%) synaptophysin-IgG-positive OIPN patients had neuropathic pain. Electrodiagnostic studies showed demyelinating or mixed axonal and demyelinating polyradiculoneuropathy features in 12 of 15 (80%) OIPN patients. Synaptophysin-IgG-positive patients had a higher median neuropathy impairment score compared to negative cases (16 vs 4; p=0.019). Among synaptophysin-IgG-positive IPN cases, 67% had demyelinating/mixed axonal-demyelinating electrophysiology, and all but one patient reported neuropathic pain. Nearly all synaptophysin-IgG IPN cases who received immunotherapy and/or cancer-directed therapy (7/9, 78%) showed improvement, except two patients who passed away due to advanced malignancy.

Conclusion: Our findings identify synaptophysin- and GAP43-IgG as biomarkers of an immunotherapy-responsive IPN.

#1203 Autoimmune nodopathy with anti-neurofascin 186 antibody presenting with asymmetric hand weakness and tongue fasciculations

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Introduction: Autoantibodies against nodal/paranodal regions of myelinated fibers can cause autoimmune polyneuropathies. Nodopathies associated with anti-neurofascin186 (NF186) antibodies can present with an asymmetric distal-predominant sensorimotor polyneuropathy, sometimes with cranial mononeuropathies.

Methods: CASE REPORT

Results: A 38-year-old man presented with insidious onset of asymmetric hand weakness, which slowly progressed over 18 months, most severe in finger and wrist extensors. Mild left upper extremity numbness and prominent tongue weakness affecting speech and swallowing developed. Left hemi-tongue atrophy and fasciculations were present on examination. Initial evaluation showed a negative GM1 antibody and unremarkable brain and cervical spine MRI. Nerve conduction studies did not show demyelinating features. Needle electromyography in weak muscles showed increased insertional activity; motor unit morphology was of low amplitude, short duration and often increased polyphasia. Biopsy of the left extensor carpi radialis longus muscle showed neurogenic changes. Genetic testing for Kennedy's disease was negative. IVIG was started, resulting in rapid improvements of symptoms and signs, and continued ever 4 weeks for close to 8 years. Attempts at lowering the IVIG dose resulted in clinical worsening. At the age of 48, he developed DVT/PEs after a series of long car drives. IVIG was stopped. Rituximab was considered but per patient preference, mycophenolate mofetil was started instead. Strength examination continued to improve though rare tongue fasciculations returned. Additional laboratory testing revealed a positive NF186 IgM antibody.

Conclusions: Nodal/paranodal neuropathies can mimic motor neuronopathies. Antibody testing should be considered for motor predominant peripheral processes to assess for treatment-responsive immune-mediated neuropathies.

#1198 Development of a consensus minimum data set for motor neurone disease

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Introduction: Analysis of large datasets is crucial for advancing our understanding of rare neurological disorders such as motor neuron disease (MND) and guiding health policy. Minimum Data Sets (MDS) define the essential data elements for clinical and research use, enhancing data comparability and generalisability. This standardisation is especially important for rare diseases due to limited patient numbers. However, most neurological disorders currently lack a consensus MDS.

Objectives: We aim to develop a consensus-driven MDS for MND. To support this, we conducted a systematic review of the data items collected across existing MND registries and databases.

Methods: A systematic review (PROSPERO ID CRD420250654180) searched MEDLINE, CINAHL, Academic Search Ultimate, Embase, and CENTRAL up to January 14th, 2025, limited to English and human studies. We included observational registries/databases of adults (≥16 years) diagnosed with MND by consensus criteria. Additional searches of clinicaltrials.gov and Google identified ongoing trials and grey literature. Extracted data covered registry/database design, data acquisition methods, and collected data elements.

Results: We identified more than 50 MND registries/databases worldwide, with wide variability in the data items collected. Furthermore, even registries within the same country lacked consensus on the data items included.

Conclusions: Variability in data collection across MND registries/databases limits large-scale analyses. Consensus MDS can enhance our understanding of rare neurological diseases through standardised data collection and analysis. Future work will focus on creating a consensus-based MDS for MND by engaging with clinicians and patients/caregivers in structured meetings, using a consensus method known as the Nominal Group Technique.

#1362 Maximizing Efficiencies in Clinical Trials: An Integrated Model for Accelerated Therapeutic Development

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Introduction: Drug development is lengthy, expensive, and filled with operational inefficiencies that hinder timely therapeutic advancement.

Objectives: To describe how an academic university tertiary medical center has implemented an integrated research and operational model that is designed to maximize efficiencies and accelerate therapeutic development for rare neurological diseases compared to standard clinical trial operational models.

Methods: The approach combines specialized research units with focuses on clinical trials coordination, clinical materials services, responsive patient-reported outcomes, technology research and innovation, data modeling and predictive analytics, and community health. This structure supports the full research lifecycle, from protocol development through full regulatory approval.

Results: This integrated model has supported over 155 clinical studies and enrolled more than 45,000 participants worldwide. The specialized, collaborative structure has contributed to the approval of 12 FDA-approved medications and devices across multiple diseases. Access to disease experts, academic affiliation, regulatory readiness, ability to conduct decentralized trials including sensors and technology, and deep experience in study design have yielded operational benefits including reduced study start-up time, improved participant recruitment and retention, efficient drug supply management, robust forecasting, safety monitoring, sensitive therapeutic benefit detection, faster data analysis with enhanced data quality, and streamlined interactions with regulatory agencies.

Conclusions: When properly designed, an integrated departmental model such as the one described reduces trial inefficiencies and enhances study outcomes, offering a multicenter framework that scientifically explores the benefits of therapeutic interventions while maximizing clinical trial effectiveness.

#1164 LEOPARD-DMD: 6-Month Results from a 2-Year Natural History Study of Adults and Children with Duchenne Muscular Dystrophy

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Introduction: To further advance DMD therapeutic development and clinical care, there is a need to better understand how DMD disease burden changes over time and determine the performance metrics of existing DMD instruments. Previously, we developed and validated the regulatory-grade DMD-HI and the caregiver-reported DMDCR-HI to quantify clinically-meaningful changes in DMD health overtime.

Objectives: To conduct a 24-month, remote, longitudinal study with caregivers and individuals with DMD to evaluate how disease burden changes overtime and identify factors associated with a faster or slower progression of disease.

Methods: Individuals with DMD and caregivers completed the DMD-HI, DMDCR-HI, and additional questionnaires at 6-month intervals. We analyzed: 1) How multifactorial DMD disease burden changes over time; 2) The minimal clinically important difference of the DMD-Health Indexes; 3) Factors associated with progression of disease; and, 4) Participant instrument preferences.

Results: We enrolled 36 individuals with DMD (age: 21.8 years (11 to 49)) and 92 DMD caregivers (reporting on behalf of patients 12.3 years (2 to 21)). Using the DMD-HI, patients identified a worsening of their shoulder and arm function over 6 months (9.94 points, p-value: 0.0349). Compared to the PedsQL, participants identified the DMD-HI and the DMDCR-HI as addressing the most important symptoms in DMD, being better suited to detect important changes in the disease, and preferable for use in clinical trials.

Conclusions: Multifactorial disease burden is slowly progressive in DMD and can be quantified using the regulatory-grade DMD-HI and DMDCR-HI.
Funding: This research is being funded by the Muscular Dystrophy Association (MDA)

#1155 Foot ulceration in patients with Charcot-Marie-Tooth Disease: evaluation of patient access to podiatry services

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Introduction: Patients with Charcot-Marie-Tooth (CMT) disease and related disorders have an increased risk of foot ulceration, which can lead to significant morbidity. Timely and effective podiatry care plays a key role in prevention and management; however, data on patient perspectives regarding the accessibility and effectiveness of podiatry services are limited.

Objectives: To evaluate patient perspectives and satisfaction with podiatry services, focusing on accessibility, service effectiveness, and their role in preventing and managing foot ulcers in the United Kingdom (UK).

Methods: We conducted an audit using a questionnaire addressed to CMT patients attending our genetic neuropathy clinics.

Results: Ninety-three patients with CMT and related disorders completed the questionnaire (55% female; mean age 48 years, range 18–79). Eight (9%) reported ulcers at the visit. Most (80, 86%) had CMT, mainly CMT1A (46/80) due to PMP22 duplication. Ten (11%) had hereditary sensory neuropathy (HSN), with 6/10 having HSN1 due to SPTLC1/SPTLC2 variants. Of respondents, 60% (56/93) were advised to use podiatry services, but only 25% (23/93) accessed them. Seven attended private podiatry. Access was influenced by healthcare referral (42%) and appointment availability (37%). Barriers included long waiting times (18%) and limited local services (17%). Among 49/61 (80%) who used podiatry, most felt it improved foot health. However, 60% (56/93) were unsure or unaware of podiatry's effectiveness in preventing foot ulcers in CMT.

Conclusions: These findings highlight significant gaps in podiatry service delivery for individuals with CMT and related disorders. Improved service provision and patient education are critical to enhancing preventive care and reducing foot ulcer complications in this population.

Comorbidities, medication use, and adverse events in FSHD patients: Insight from the Resolve and Move studies

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Introduction: As treatment options for facioscapulohumeral muscular dystrophy (FSHD) expand, data on associated comorbidities remain limited.

Objectives: To evaluate comorbidities, medication use, and adverse events (AEs) in FSHD patients enrolled in the Resolve and Move natural history studies.

Methods: Participants were enrolled in two large natural history studies (Resolve: n=303; Move: n=404). Comorbidities were self-reported; medications were categorised by use, and adverse events tracked during the study.

Results: In Resolve (mean age 50.3), common comorbidities included vision problems (22%), pulmonary issues (19%), hearing problems (17%), and cardiovascular conditions (14%). In Move (mean age 47.3), comorbidity rates were similar: vision (23%), pulmonary (25%), hearing (16%) and cardiovascular (19%). Use of breathing devices was highly prevalent in both Resolve and Move (44% and 52 % of participants with pulmonary issues). The most frequently used medications in both studies were supplements (Resolve 33%, Move 39%) and pain management medications (Resolve 26%, Move 25%). Most analgesics were taken for FSHD-related pain, with non-steroidal anti-inflammatory drugs (NSAIDs) being the most commonly reported pain medications. Adverse events (AEs) were reported by 21% (65/303) of Resolve participants and 8% (32/404) of Move participants. The most common AEs were musculoskeletal symptoms or injuries (Resolve 65%, Move 41%), falls (Resolve 35%, Move 6%), and blood draw-related issues such as bruising (Resolve 22%, Move 12%).

Conclusions: Cardiovascular and pulmonary comorbidities were reported in a significant proportion of patients. Breathing device use was also common, including individuals likely to be eligible for clinical trials (Resolve cohort). Analgesic and supplement use was high in people with FSHD.

#1150 Exploring perceptions, barriers and facilitators to physical exercise in congenital myasthenic syndromes

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Introduction: Congenital myasthenic syndromes (CMS) are a clinically and genetically heterogeneous group of disorders characterized by impaired neuromuscular transmission, leading to exercise-induced weakness and fatigability. To the best of our knowledge, no study has explored exercise perceptions in individuals with CMS.

Objectives: Our study aimed to explore perceptions of exercise and to identify barriers and facilitators to exercise among adults with CMS living in France.

Methods: A purpose-built online questionnaire was created and diffused including validated PROs. Exercise was defined as an activity that is structured, planned, repetitive, voluntary and active, with the aim of improving or maintaining one's health.

Results/Conclusions: Thirty participants responded, of whom 21(70%) were female, median [IQR] age 42 years [33-52], BMI 24[19-26], disease duration 12.5 years [7-22]. Thirteen participants (43.3%) reported engaging in exercise, while 17 declared that they do not (non-exercisers). Those that exercise reported having more stable disease (p=0.007) and were more frequently satisfied with their current symptom state (PASS) compared to non-exercisers (p<0.001). Non-exercisers reported greater fatigue (p =0.012), reduced HRQoL (p<0.001) and greater impact of SMC on ADLs (p=0.007). In terms of beliefs, non-exercisers were more likely to believe that exercise is contra-indicated (p = 0.0.025) and reported greater fear of exercising (p = 0.009) compared to exercisers. Most non-exercisers (88.2%) reported a desire to exercise, citing upper limb, lower limb and neck symptoms as the main CMS-related obstacles. The primary barrier, reported by 76.5%, was a lack of "specialised" coaching. The second most frequent barrier, reported by 41.2%, was the fear of the consequences of exercise on their symptoms or disease.

#1143 A Phase 2, Open Label Trial of Repeated Intrathecal Autologous Adipose-Derived MSCs in ALS

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Introduction: Mesenchymal stromal cells (MSCs) are being developed as a treatment for ALS and are hypothesized to exert their effects via growth factor secretion and immunomodulation.

Objectives: In this Phase 2 open label clinical trial, we aim to evaluate the safety and efficacy of repeated intrathecal autologous adipose-derived MSCs in people living with ALS.

Methods: After a 3-month lead-in pre-treatment period, participants receive up to 4 treatments (10-100 x 10^6 MSCs), spaced 3 months apart. Efficacy endpoints include comparison of the pre-treatment and post-treatment ALSFRS-R slopes. A secondary responder analysis is defined as a >25% improvement in ALSFRS-R slope between pre-treatment and treatment periods.

Results: 75 participants were enrolled, and 57 were fully accrued with at least one treatment and post-treatment follow-up (analysis group). Mean (range) age of the analysis group was 56 (28-77) with a male predominance (70%). The mean (range) ALSFRS-R at enrollment was 37 (19-47). Mean (range) baseline plasma neurofilament light chain level was 83.7 pg/mL (16.3-373.8), correlating with rate of disease progression. Intrathecal MSC therapy was generally well-tolerated with the most common adverse event being temporary back and leg pain. There was no statistical significance between the ALSFRS-R slope in the pre-treatment and post-treatment periods (p=0.38).

Conclusions: Our multi-site Phase 2 clinical trial of MSC therapy in ALS is completed. The full analysis group did not demonstrate an improvement in the ALSFRS-R slope, but post-hoc analyses are ongoing. The clinical trial endpoint data and biomarker analyses will help inform future studies of MSCs in ALS.

#1142 Upper limb progression in Duchenne muscular dystrophy: insights from a 36-month longitudinal study using the PUL 2.0

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Introduction: Duchenne muscular dystrophy (DMD) is a progressive disorder. This study evaluates upper limb function in DMD patients using the Performance of Upper Limb 2.0 (PUL 2.0) over 36-months.

Methods: Data were collected between 2011 and 2024. Patients with at least 36 months of follow-up were included. Mixed-effects models accounting for repeated measures evaluated 36-month PUL 2.0 changes by entry item and ambulatory status. The entry item assesses the overall upper limb function of the patient. Ambulant patients were defined as those able to walk 10 meters independently, transitioning patients as those who lost ambulation during the duration of the study and non-ambulant as those who had already lost ambulation at baseline.

Results: A total of 219 patients provided 684 paired 36-month assessments. Ambulatory status significantly affected total, shoulder, elbow, and distal scores at baseline. The largest 36-month decline in total scores was found in the 58 transitioning patients (11.62 points, 95%CI = -12.40,10.84), followed by non-ambulant and ambulant subgroups (n=116 and n= 86 respectively). The largest declines were seen in patients with baseline entry score of 4 (−11.97, 95% CI = -13.48, -10.46) and 5 (-11.55, 95% CI = -12.46, -10.63), with smaller declines for other entry scores.

Conclusions: The 36-month analysis confirms a clear trend of functional decline across time points, with the transitioning group exhibiting the greatest changes in upper limb function. These findings provide valuable insights for designing trials and offer a reference for long-term comparison of treatment efficacy in both experimental and real-world setting.

#1139 Serum Proteomic Profiling Reveals Acute Inflammatory Response as a Key Pathogenic Mechanism in Myotonic Dystrophy Type 1

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Introduction: Myotonic dystrophy type 1 (DM1) is a multisystemic disorder caused by CTG repeat expansion, with poorly understood systemic proteomic changes. Circulating protein biomarkers could provide insights into disease mechanisms, facilitate monitoring and shed light on new potential therapeutic targets.

Objectives: To characterize serum proteomic profiles across DM1 subtypes and identify differentially expressed proteins correlating with clinical manifestations and disease severity.

Methods: Cross-sectional proteomic analysis of serum from 35 DM1 patients (25 classic, 4 juvenile, 2 infantile, 4 congenital) versus 15 controls. Following protein depletion and TMT10plex labeling, mass spectrometry analysis was performed. Bioinformatics included Principal Component Analysis (PCA), differential expression analysis using limma with MIRS/sex covariates, and Gene Ontology enrichment.

Results: PCA revealed disease severity gradient with congenital DM1 most distinct from controls. Differential expression identified 35 significantly dysregulated proteins (adjusted $p<0.05$, $|\log_2 FC|>0.5$). Acute inflammatory response was most enriched ($p.adj=9.97\times10^{-10}$), involving 7 proteins. Classic DM1 showed pronounced inflammatory signature: ORM1, ORM2, A2M, HP, HPR significantly upregulated ($p<0.0001$), APOA2 downregulated ($p<0.001$). Congenital DM1 demonstrated severe early inflammation, juvenile DM1 intermediate changes. Disease enrichment revealed associations with acute kidney insufficiency ($p.adj=1.84\times10^{-7}$) and drug toxicity ($p.adj=1.63\times10^{-6}$).

Conclusions: This first comprehensive serum proteomic study reveals acute inflammatory response as central to DM1 pathogenesis, with subtype-specific signatures suggesting distinct mechanisms. Novel kidney and drug metabolism associations expand understanding of systemic involvement. Acute phase proteins represent promising biomarkers, identifying inflammation as a potential therapeutic target beyond RNA toxicity mechanisms.

#1138 An Audit of Bone Health Assessment in Patients with Myotonic Dystrophy

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Introduction: Myotonic dystrophy (DM) is a multisystem neuromuscular disorder associated with reduced mobility, falls, and increased fracture risk. The presence of bone abnormalities in DM is well-known but incompletely addressed in DM-specific guidelines and clinical reviews..

Objectives: To evaluate current bone health screening and management in patients with DM at the Muscle Disease Unit, Salford Royal Hospital.

Methods: A retrospective audit of electronic records over the past 10 years was performed for 60 randomly-selected DM patients attending a tertiary neuromuscular service. Data included fracture history, DEXA scan referrals, vitamin D levels, smoking status, and smoking cessation advice.

Results: Five patients had a documented fracture history; three underwent DEXA scanning, none referred by the neuromuscular team. No diagnoses of osteopenia or osteoporosis were recorded. Vitamin D levels were available for 30 patients; one with persistent deficiency was diagnosed with hyperparathyroidism. No advice on weight-bearing exercise advice was documented. Smoking status was recorded for 23 patients; two smokers were referred for cessation support.

Conclusions: Bone health assessment in DM is inconsistent, with missed opportunities for screening and intervention. Evidence of preventative advice, DEXA scans, and vitamin D monitoring remains low, with persistent deficiency poorly investigated. Recommendations include incorporating fracture risk assessments (e.g. FRAX), vitamin D testing, and lifestyle guidance into DM clinic review templates. Reviewing local practice against the Consensus Care Guidelines may standardise management in this high-risk population, though these may need updating to reflect emerging evidence about bone health.

#1129 Cochrane Review: rituximab for myasthenia gravis in adults

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Introduction: It is important to bring together high-quality evidence to determine how rituximab would be best used in treatment algorithms for MG.

Objectives: To conduct a Cochrane systematic review to assess the effects of rituximab (including biosimilar variants) for the treatment of MG in adults.

Methods: We conducted a systematic review for randomised controlled trials (RCTs) in adults (aged 16 years and over) with MG (all subtypes and severity), comparing rituximab with placebo, no treatment, or alterative therapy. We assessed potential bias of studies, and synthesised results for each outcome using meta-analysis where possible. Data were analysed on an intention-to-treat basis. We used Grade to assess the certainty of evidence for each outcome.

Results: We included two RCTs with a total of 99 participants. The study populations and treatment strategy differed; one administered rituximab at low doses in new or early-onset generalised MG, and the other at high repeated doses as add-on therapy. The evidence has limitations. Beyond 9 months, the evidence is very uncertain on the effects of rituximab on disease severity as assessed with QMG score, and functional ability as assessed by MG-ADL. The evidence suggests that rituximab results in little to no difference in its steroid-sparing effect beyond 9 months but probably results in a large reduction in relapse requiring rescue therapy (220 out of 1000 people with rituximab, compared with 490 out of 1000 people with placebo). Rituximab may reduce SAEs, but the evidence is very uncertain.

Conclusions: Though there were limitations of this review, with uncertainty regarding many of the outcomes, rituximab probably results in a large reduction in relapse requiring rescue therapy. Further studies examining B cell-depleting therapies in different MG patient subgroups are warranted.

#1124 Community Disadvantage Negatively Affects Cognitive Performance in Duchenne Muscular Dystrophy

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Introduction: Duchenne Muscular Dystrophy (DMD) is the most common neuromuscular condition affecting children. Prior work has shown that social determinants of health (SDOH) influence motor outcomes in DMD. Whether community disadvantage affects brain health in DMD remains unknown. Understanding this relationship may help clarify how environmental factors influence cognitive outcomes in families affected by DMD.

Objectives: To investigate the influence of community-level disadvantage on cognitive functioning in sons with DMD and their biological mothers.

Methods: We conducted a cross-sectional analysis of 65 sons with DMD and their biological mothers. Cognitive performance was assessed using the NIH Toolbox Cognitive Battery (NIHTB-CB). The Social Vulnerability Index (SVI), a geospatially-determined scale, was used to quantify the degree of community disadvantage experienced by each dyad.

Results: Fluid cognition scores were positively correlated between sons and mothers. Greater community disadvantage (higher SVI) was associated with poorer performance on the Flanker Inhibitory Control and Attention test among sons ($r = -0.20$) and on the Dimensional Change Card Sort (DCCS) test of cognitive flexibility among mothers ($r = -0.16$).

Conclusions: Our work shows that community disadvantage affects sons with DMD and their biological mothers. Interventions with a multipronged approach are necessary to address community disadvantage. Incorporating community-level factors into both clinical care and research may improve cognitive and developmental outcomes in families affected by DMD.

#1270 Longitudinal Psychometric Properties of the Myotonic Dystrophy Health Index in a large multicentric cohort of people living with Myotonic Dystrophy Type 1.

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Introduction: The MDHI is a validated patient-reported outcome measure to assess disease burden in DM1. Although widely used in industry trials, further data on its longitudinal performance can enhance its interpretation in future studies.

Objectives: The aim of this study is to assess MDHI sensitivity to change and responsiveness.

Methods: Adult DM1 patients were enrolled in a 24-month longitudinal observational study (END-DM1). Confirmatory internal consistency and external validity were assessed. MDC was estimated using SEM and Esch, while MCID was calculated using anchor-based method based on the Domain Delta questionnaire. Sensitivity to change was analyzed through change scores; moreover, stratification into quartiles based on changes in MDHI total and short form (SF) scores was also performed to compare baseline subdomain scores and clinical variables, in order to identify predictors of disease burden trajectory. Responsiveness was assessed by comparing clinical outcomes across groups defined by MDHI score direction (improved/stable vs worsened).

Results: Of 451 DM1 patients assessed cross-sectionally, 147 completed 24-month follow-up. Internal consistency (Cronbach's $\alpha = 0.95$) and external validity were confirmed. MDC for total score was ±9.72 (SEM) and ±4.24 (ESch); subscale MDC ranged from ±12.62 to ±27.17 (SEM) and ±6.04 to ±12.70 (ESch). Quartile analysis showed baseline differences in specific subscales and motor/respiratory status among groups, suggesting predictive value. Changes in MDHI scores aligned with clinical outcomes, confirming responsiveness.

Conclusions: The MDHI shows strong longitudinal validity, sensitivity to change, and responsiveness in DM1. Specific subdomains and baseline motor/respiratory status may predict long-term burden, supporting MDHI's utility in clinical trials and natural history studies.

II. Genetic and Molecular Studies

#1272 Clinical and Genetic Characterization of Patients with Pathogenic Mitochondrial DNA Duplications

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Introduction: Mitochondrial DNA (mtDNA) duplications have been reported anecdotally and are associated with myopathy, multisystem phenotypes, Kearns–Sayre syndrome, and, in some cases, normal aging. However, in the absence of large cohort studies, the clinical spectrum and genotype–phenotype correlations of mtDNA duplications remain poorly defined.

Objectives: To characterise the clinical manifestations of patients with mtDNA duplications managed at the NHS Highly Specialised Service for Rare Mitochondrial Disorders in London.

Methods: Clinical data and laboratory investigations of patients with confirmed mtDNA duplications were retrospectively reviewed.

Results: Nine patients were identified, including three males and six females, aged 15 to 63 years (mean: 40). Six patients had pathogenic variants in MT-ND1, MT-TS1, MT-CO1, MT-ND2, or MT-ND1 combined with MT-CYB. Seven out of nine patients had a positive family history. Lactate (n=7) ranged 1.40–2.82 mmol/L (median 1.46), CK (n=6) ranged 116–733 U/L (median 318). Clinical features included diabetes and hearing loss (each 78%), vestibular dysfunction, ptosis, and fatigue (each 44%), ataxia and external ophthalmoparesis (each 33%), retinal dystrophy (22%), and proximal weakness (11%). Two patients had cardiac arrhythmias, one requiring a pacemaker. Age at symptom onset ranged 6–29 years (mean 14), with diabetes (67%) or hearing loss (33%) as initial presentations. One patient developed bone marrow aplasia; another showed MRI findings suggestive of mitochondrial leukodystrophy.

Conclusions: mtDNA duplications manifest as a multisystem disorder, often consistent with the MIDD phenotype. Unlike typically sporadic single deletions, mtDNA duplications are more commonly maternally inherited. Onset usually occurs in childhood, unlike point mutations. Although less frequent, cardiac and hematological manifestations may necessitate close surveillance.

#1271 Clinical Masks of a Rare Mitochondrial Disorder: A Case Study of Kearns-Sayre Syndrome

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Introduction: Kearns-Sayre syndrome (KSS) is a rare, progressive neuromuscular disorder resulting from deletions in mitochondrial DNA (mtDNA). KSS is characterized by a classic triad of progressive external ophthalmoplegia, pigmentary retinopathy, and disease onset before 20 years old.

Methods: Case Report

Results: A 15 year old male patient was admitted to the Neurological ward with suspected Myasthenia gravis (MG). He reported a history of asymmetrical bilateral ptosis, fatigue, and depression. MG was excluded by repetitive nerve stimulation and antibody testing. MRI scans of the head and chest displayed no abnormalities. Cerebrospinal fluid testing revealed elevated protein concentration. Ophthalmological examination demonstrated “salt and pepper” pigment rearrangements on the retina, raising suspicion for KSS. A cardiological examination revealed supraventricular beats with no other abnormalities. Genetic testing (MLPA) identified low heteroplasmy of the mitochondrial mutation and long PCR suggested the presence of a large-scale mtDNA deletion. The patient was discharged home with supplementation of Coenzyme Q10, L-carnitine, vitamin C, D, B-complex, and Sertraline.

Conclusions: The broad range of multi-systemic manifestations of KSS and the clinical overlap with other conditions complicated the diagnostic process. In this case, bilateral ptosis was initially attributed to the patient’s known inhalant allergies, subsequently raising suspicion for MG. The diagnosis was prolonged four years due to the patient’s complex history, low prevalence of KSS, and the restricted access to healthcare during COVID-19. This case highlights the complexity associated with diagnosing KSS, particularly with atypical presentation.

#1263 Duchenne Muscular Dystrophy; Not Just a Carrier

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Introduction: Duchenne muscular dystrophy (DMD) is a rare X-linked recessive neuromuscular disorder that predominantly affects males, approximately 1:5,000 live male births due to pathogenic variants in the DMD gene. Symptomatic presentation in females is very rare, approximately 12% of female carriers, and typically associated with skewed X-chromosome inactivation favoring expression of the mutant allele.

Methods: Case Report

Results: An 8-year-old female presented with episodic myalgias, persistently elevated creatine kinase (CK) (peak CK 3950 IU/L), and mild proximal muscle weakness for a few months. Her medical history included attention-deficit disorder, with no reported trauma or excessive physical exertion. Family history was non-contributory. Neurologic examination raised concern for an underlying myopathy. Electromyography revealed a diffuse myopathic pattern. Genetic testing was performed and confirmed DMD with heterozygous pathogenic nonsense variant in the DMD gene (c.9568C>T, p.Arg3190*). X-inactivation studies demonstrated a skewed pattern (83:17) favoring expression of the mutant allele. A muscle biopsy revealed: myopathic features with decreased dystrophin sarcolemma reactivity in both mid rod and carboxy terminus domains.

Conclusions: This case highlights the diagnostic complexity of DMD in females and the importance of considering X-linked conditions in females with elevated CK and muscle weakness. Integration of clinical manifestations and genetic testing are essential in establishing diagnosis and guiding care. Early recognition in female patients is critical, as it could represent a diagnostic dilemma and may potentially offer treatment options in the context of new advancement of available therapies.

#1247 100 Adults with Spinal Muscular Atrophy at the Dawn of Treatment: A Bone Health Focus

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Introduction: As disease-modifying treatments for spinal muscular atrophy (SMA) are implemented, co-morbidities in adults including osteo-pathologies are increasingly recognised. Guidance for managing such issues is incomplete. We present data on bone health from, to our knowledge, the UK's largest single-centre adult SMA cohort.

Objectives: We aimed to quantify the following bone heath specific parameters in our cohort:
1. Fracture incidence and type
2. Implementation of bone density scanning
3. Cholecalciferol status and supplementation

Methods: Data was prospectively recorded for 100 patients (51% male; 49% female, average age 32), at the National Hospital for Neurology and Neurosurgery from 2022-2025.

Results: SMA subtypes were SMA3 (55%), SMA2 (44%) and SMA1 (1%). Where available ethnicities were: White (n=57), Asian (n=13), Black (n=4), Mixed (n=2) and Other (n=4). Fracture incidence was 23%, of which 82% affected the lower limb(s). Most fractures (78%) occurred in SMA3 patients who have been ambulant. However, 55% of these patients have since lost the ability to ambulate. Bone density scans were recorded in 39% of patients who had fractures (89% of scans occurred post fracture). Bone density scans were recorded in 11.7% of non-fracture patients. Of the overall cohort, 39% were vitamin D deficient/insufficient, and 60% prescribed cholecalciferol.

Conclusions: The high fracture rate is particularly pertinent, given that lower limb fractures can accelerate ambulation loss in SMA3 patients. Consistency in bone-density scanning is lacking and generally reactive to fracture occurrence. Overall, this highlights the importance of bone health considerations in SMA patients.

#1245 BSCL2-Associated Distal Hereditary Motor Neuropathy Presenting with Split Hand

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Introduction: Distal hereditary motor neuropathies (dHMNs) are a genetically and phenotypically diverse group of disorders. Recognizing a patient's weakness pattern can guide targeted testing and diagnosis. We report a case of BSCL2-associated dHMN presenting with a split hand pattern, expanding the clinical spectrum of BSCL2-related disorders.

Methods: Case Report. Clinical data was retrospectively reviewed through the electronic medical record. Written informed consent was obtained from the patient.

Results: A 49-year-old right-hand dominant woman presented with 4 years of bilateral hand weakness without sensory symptoms. She had a history of isolated right hand weakness at age 22, diagnosed as carpal tunnel syndrome and treated surgically, with reported symptom stabilization. On evaluation, she had marked atrophy and weakness of the abductor pollicis brevis (APB) and first dorsal interosseous (FDI) muscles bilaterally, with mild weakness but preserved bulk of the abductor digiti minimi (ADM)—consistent with a split hand pattern. The remainder of her neurologic exam, including tone and reflexes, was normal. Electrodiagnostic studies demonstrated a chronic neurogenic process affecting the bilateral C8 and T1 myotomes, with ongoing denervation and without conduction block. Magnetic resonance imaging of the cervical spine and brachial plexus bilaterally was unremarkable. She was treated with intravenous immunoglobulin for possible multifocal motor neuropathy without benefit. Genetic testing confirmed a heterozygous pathogenic mutation in BSCL2.

Conclusions: This case expands the phenotypic presentation of BSCL2-associated dHMN to include split hand. BSCL2 mutations should be considered in patients presenting with progressive distal upper extremity weakness and split hand pattern.

#1244 100 Adults with Spinal Muscular Atrophy at the Dawn of Treatment: Demographics and Treatment Use

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Introduction: Spinal muscular atrophy (SMA) is an autosomal recessive disorder characterised by progressive muscle weakness and multisystem impairments. Until recently, SMA was managed supportively. However, from 2019-2020, 2 disease-modifying therapies (Nusinersen and Risdiplam) were licensed for treatment in the UK.

Objectives: We present the UK's largest single-centre adult SMA cohort, highlighting treatment details, respiratory function, feeding support and reproductive health.

Methods: Data was prospectively recorded at the National Hospital for Neurology and Neurosurgery (NHNN) between 2022-2025 for 100 patients (51% male; 49% female; average age 32).

Results: SMA subtypes: 55% SMA3, 44% SMA2, 1% SMA1 and no SMA4. Where available, ethnicities were: White (n=57), Asian (n=13), Black (n=4), Mixed (n=2) and Other (n=4). 89 patients were treated at NHNN (including 2 stopping treatment) with 5 pending initiation and 6 treated elsewhere. More NHNN patients on active treatment (n=87) use Risdiplam (77%) than Nusinersen (23%). Notably, 95% of patients adhered to their original treatments, with only 3 switching interventions. Reviewing respiratory support, 43% used non-invasive ventilation, with 3 requiring tracheostomies. 45% utilised cough-assistance devices. Where available (n=76), mean functional vital capacity was 2.58L (0.41L-6.57L). 15% of the cohort had biological children- 9 were male and 6 female. Reviewing dietary support, 14% had gastrostomies-in-situ and 18% used Therabite devices. Where available (n=72), average body mass index was 22.8 (10.2-41.0).

Conclusions: Our results demonstrate heterogeneity in demographics, treatment use and respiratory/nutritional support. Excellent treatment adherence implies Risdiplam and Nusinersen are well-tolerated. We believe highlighting this variability enables scope for holistic approaches to long-term SMA management.

#1240 Altered BCR signaling mediates defects in early B cell tolerance checkpoints: insights from single cell analysis of NF155-mediated autoimmune nodopathies

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Introduction: Autoimmune nodopathies (AINs) are associated with autoantibodies (often of immunoglobulin G subclass 4 (IgG4)) against the node of Ranvier proteins with distinct clinical features.

Objectives: In this study, we examined if there is a breach in early B cell tolerance in neurofascin-155 mediated AIN (NF155-AIN), and we leveraged single-cell transcriptomics to understand the potential pathomechanism of such a breach.

Methods: Recombinant monoclonal antibodies derived from new emigrant and mature naïve B cells of NF155-AIN patients and healthy controls (HCs) were tested for polyreactivity using a well-established assay. Then, we examined the transcriptional expression of peripheral blood mononuclear cells (PBMC), with a special focus on B naïve cells and CD4+ T cells at the single-cell level.

Results: NF155-AIN patients have higher fractions of polyreactive B cells in the new emigrant/transitional (37.4% compared to 10.5% in HCs, $p = 0.025$) compartment as well as in the mature naïve (31.5% compared to 8.9% in HCs, $p = 0.021$) compartment. B cell clones expressing anti-nuclear antibodies (ANA) were also higher in NF155-AIN compared to HCs. Such breach in B cell tolerance is potentially mediated by abnormal B cell receptor (BCR) signaling with low CD79B, CSK, BLNK, and BTK expression. Furthermore, the low expression of TCL1A and WAS implicated abnormal B cell development in NF155-AIN. We also observed impaired CD4+ T cell regulation, which may limit the suppression of autoreactive B cells. Moreover, comparison with chronic inflammatory demyelinating polyneuropathy (CIDP) patients confirmed that such differences are specific to NF155-AIN.

Conclusions: There is an early B cell tolerance checkpoint defect in NF155-AIN, potentially mediated by impaired BCR signaling and abnormal B cell development.

#1230 An omics-based investigation of changes at the molecular level in differing severities of Spinal Muscular Atrophy

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Introduction: Spinal muscular atrophy (SMA) is classified on developmental milestones reached with severity ranging from Type 0 to IV. Current genetic therapies alter disease progression but are not curative. Treatments show promise for children with severe SMA but are generally less effective for adults with less severe SMA.

Objectives: To determine whether the proteomic and transcriptomic profiles of SMA varies according to severity.

Methods: Fibroblasts (Types I-III), iPSCs (Type I-III) and myoblasts (Type III) from individuals with SMA were expanded in culture. Protein was extracted from all cells and RNA extracted from iPSCs (Type I & II) and Type III myoblasts. Following proteomic and gene expression evaluation, datasets were filtered and significant changes in protein (>1.2-fold) or gene expression (>0.5-fold) calculated compared to age-matched controls.

Results: Significantly altered proteins common to each SMA severity: Type I, five proteins; Type II, two proteins; Type III, one protein. No significantly changed protein or gene was common to all severities, but 21 genes were similarly altered in SMA Type I and II. Bioinformatics found “Biosynthesis”, “Cardiovascular Signalling”, “Cellular Stress & Injury”, “Cellular Growth, Proliferation & Development”, “Intracellular & Second Messenger Signalling” and “Signal Transduction” to be significantly impacted in both ‘omics datasets for all SMA severities. The “Warburg Effect Signalling Pathway” was unique to all Type I datasets and “Ephrin-B Signalling” unique to the Type III proteomic datasets.

Conclusions: This work furthers our understanding of the impact at the molecular level of SMA and highlights the potential need to consider development of severity-specific therapies for SMA.

#1190 Changes in timed items in DMD Patients Amenable to Skipping Exons 44, 45, 51 and 53: A 24-Month collaborative study

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Introduction/Objective/ Methods: This study explored 24-month changes in motor function among 458 ambulant boys with genetically confirmed Duchenne muscular dystrophy (DMD), using two timed items: 10-meter walk/run (10MWR) and time to rise from floor (TRF). Participants were recruited from Italian, UK, and Spanish networks and assessed at baseline, 12, 18, and 24 months.

Results: When exon-skipping subgroups were examined the 10MWR were overall stable, with minimal differences across skipping subtypes. In boys ≥7, all exon categories showed functional decline, with exon 51 showing the greatest deterioration. The TRF in contrast showed an increase in TRF, indicating a functional deterioration in both age groups across all exon categories with a more severe increase in boys ≥7, particularly for exons 51 and 53.

Conclusions: Overall, the results show a different trend in the two timed items. On one hand, the 10WR showed a profile consistent with previous reports in NSAA and 6MWT with overall stable results below the age of 7 years and little differences across skipping subgroups. On the other hand, in the TRF the deterioration could already be observed in the younger group and became more marked in the older ones. These findings emphasize the variability in early disease progression in boys with DMD.

#1189 Compound Heterozygous COA7 Mutations in Two Siblings with Mitochondrial Neuropathy: A Novel Variant and Deep Clinical Phenotyping

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Introduction: COA7 (cytochrome c oxidase assembly factor 7) gene mutations are a rare cause of mitochondrial disease, with limited clinical descriptions and high phenotypic variability.

Objectives/Methods: Herein we report two siblings, brother and sister, carrying compound heterozygous COA7 variants—one of which is novel—presenting with early-onset, slowly progressive axonal sensorimotor neuropathy.

Results: The elder brother first exhibited symptoms at the age of 12, including muscle cramps, tremors and falls. The younger sister had signs of motor impairment with difficulty walking and running since the age of 5. While both siblings shared some common features, including distal weakness impairing gait, areflexia, tremor, pes cavus, sensory disturbances, and mild cognitive impairment, the older boy had an overall milder phenotype with the sister having more marked cerebellar signs. Electroneurography revealed reduced compound muscle and sensory nerve action potential amplitudes with preserved distal motor latencies, consistent with sensorimotor axonal polyneuropathy. Genetic testing identified biallelic COA7 variants (c.115C>T; p.Arg39Trp and c.457C>T; p.Leu153Phe), the latter not previously reported. Skin biopsy showed reduced activity of mitochondrial complex IV (cytochrome c oxidase). Brain MRIs in both siblings were unremarkable.

Conclusions: Our cases suggest that in presence of a slowly progressive neuropathy, mild cognitive signs, with normal neuroimaging, a possible mitochondrial dysfunction correlated to COA7 variants should be taken into account in the differential diagnosis. This report expands on the underrecognized phenotypic spectrum of COA7-related disorders, which may overlap with hereditary motor and sensory neuropathies. The identification of a novel variant and the extended clinical follow-up provide further insights into this emerging mitochondrial phenotype and highlight the importance of broad genetic screening in chronic, unexplained neuropathies.

#1180 Characterizing PMP22 proximal partners in a Schwann cell model of Charcot-Marie-Tooth disease type1A

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Introduction: Charcot-Marie-Tooth disease 1A (CMT1A) is caused by PMP22 gene duplication leading to peripheral myelin protein 22 overexpression in Schwann cells. This results in myelin sheath defects and axonal loss, leading to muscle weakness and wasting.

Objectives: To produce a stably transfected, clonal, immortalized human Schwann cell model of CMT1A and to identify potential targets for therapy design to promote degradation or enhanced PMP22 trafficking.

Methods: Human immortalised Schwann cells were stably transfected with PMP22 and a biotin ligase (BioID2) tag for labelling and identification of PMP22 proximal proteins using mass spectrometry.

Results: Mitosis was reduced in PMP22 transfected cells compared to controls, with the PMP22 fusion protein concentrated in cytoplasmic aggregates and at the plasma membrane. Addition of NRG1 and forskolin to cultures lead to upregulation of myelination potential markers in control cells, but there were more variably expressed in PMP22 transfected cells. Using BioID2, >200 proteins were identified in the proximity of overexpressed PMP22 that were undetected in control pull-downs, including integrins alpha-2 and alpha-7, which play a role in myelination via interactions with the extracellular matrix.

Conclusions: Over expression of PMP22 at the plasma membrane may alter the ability of integrins to bind to the extracellular matrix, which may in part explain dysregulated myelination seen in CMT1A. Identification of proteins in proximity of overexpressed PMP22 has generated insights into potential pathological mechanisms associated with CMT1A. Future work aims to determine whether these proteins represent targets for therapy design aimed at promoting degradation and enhanced trafficking of PMP22.

Acknowledgement: Supported by the RJAH Orthopaedic Institute (RPG193).

#1157 TDP-43 pathology induces CD8 T cell activation through cryptic epitope recognition

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Introduction: Aggregation and nuclear depletion of the RNA binding protein TDP-43 are crucial pathological features of amyotrophic lateral sclerosis (ALS) and inclusion body myositis (IBM). The loss of TDP-43 nuclear function results in the aberrant inclusion of cryptic exons in mRNA transcripts, leading to the expression of de novo proteins. Clonally expanded and highly differentiated CD8+ T cells have been observed in individuals with TDP-43 proteinopathies. However, the target antigens mediating T cell activation have remained elusive.

Objectives: Here, we investigate whether the de novo proteins induced by aberrant cryptic splicing due to TDP-43 nuclear loss can act as neo-antigens.

Methods: RNA-sequencing, immunohistochemistry and proteomics were used to identify TDP-43 cryptic peptides and immune gene enrichment in patient samples. TetTCR-SeqHD, a high-throughput and multidimensional single T cell profiling approach, was used to characterize the specificity, clonality and activation of T cells.

Results: We detect the HDGFL2 cryptic peptide and multiple other TDP-43 cryptic exons in IBM skeletal muscle, where their presence correlates with enrichment of T cells and MHC-I antigen presentation. Furthermore, we identify epitopes from HDGFL2 and IGLON5 cryptic peptides which are recognized by clonally expanded and functionally differentiated CD8+ T cells in ALS and IBM Patients. Finally, we demonstrate that T cells engineered to express the identified TCRs can activate in response to the cryptic peptides and are able to kill TDP-43 deficient cells.

Conclusions: This work identifies for the first time specific T cell antigens in ALS and IBM, directly linking adaptive immune response to TDP-43 pathology.

#1145 Muscle involvement in women carrying pathogenic DMD gene variants: a 6.5-year follow-up study

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Introduction: Women carrying pathogenic DMD gene variants can develop muscle affection, such as muscle weakness and fat replacement. The long-term progression of the muscle involvement is unknown.

Objectives: This study investigates the 6.5-year changes in muscle function and -fat fraction in women carrying pathogenic DMD gene variants, to enhance our understanding of disease progression and its natural history.

Methods: Muscle structure and -function were investigated at baseline and after 6.5 years in 34 women carrying a pathogenic DMD gene variant (20 predicted to confer Duchenne Muscular Dystrophy (DMD), 14 Becker Muscular Dystrophy (BMD)). After a clinical evaluation, muscle fat fraction was assessed using Dixon MRI, muscle strength with isokinetic dynamometry, and muscle biomarkers with blood samples for creatine kinase and myoglobin.

Results: Muscle fat fraction in the lower back, thigh, and calf increased significantly over 6.5 years. The average increases were generally less than 2%, but some carriers with significant baseline abnormalities experienced a more substantial increase in fat fraction, reaching as high as 31%. Although overall disease progression did not differ significantly between DMD and BMD carriers, all women who showed rapid progression were DMD carriers. Small but significant changes occurred in muscle strength and biomarkers.

Conclusions: The progression of muscle involvement in women carrying pathogenic DMD gene variants is generally slow. However, those with severe baseline abnormalities on MRI—often associated with a lower age of symptom onset—experience a more rapid progression of muscle fat fraction, suggesting that baseline MRI findings could help predict future disease progression in this population.

#1121 Implications of the central hinge on microdystrophin gene therapy

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Introduction: Several microdystrophins are in clinical trials to treat Duchenne muscular dystrophy. The full-length dystrophin protein has four hinges (H1, 2, 3, and 4). All microdystrophin contains H1 and 4. Some microdystrophins carry an additional central hinge (H2 or 3). However, the functional implication of the central hinge is unknown.

Objectives: This study aims to determine whether including a central hinge in microdystrophin influences the therapeutic outcome in the mdx mouse model.

Methods: Two microdystrophins were engineered. They are identical except that one has a central hinge and the other does not. Microdystrophins were packaged in AAV9 and delivered to 2.5-m-old mdx mice via the tail vein at 4E+14 vg/kg. Four months after the AAV injection, we evaluated microdystrophin expression, AAV vector genome copy number, ECG, forelimb grip strength, serum CK, and histology and function of the tibialis anterior (TA) muscle.

Results: Both vectors resulted in saturated microdystrophin expression and equivalent vector genome copy numbers in the TA muscle and heart. Both vectors also yielded similar improvement in serum CK, grip strength, and TA muscle histology and force. However, the one without the central hinge showed better protection against eccentric contraction-induced damage in the TA muscle. Further, this vector significantly reduced tachycardia.

Conclusions: Our results suggest that the central hinge is not necessary for microdystrophin function. Removing the central hinge may have a beneficial effect.

#1094 Unraveling Biomarkers for Postural Orthostatic Tachycardia Syndrome (POTS): A Proteomics-Driven Discovery

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Introduction: Postural Orthostatic Tachycardia Syndrome (POTS) is a debilitating autonomic disorder characterized by excessive heart rate increase upon standing. Despite its clinical significance, reliable biomarkers for diagnosis and prognosis remain unidentified. Advances in proteomics provide a promising avenue for discovering novel biomarkers to enhance diagnostic accuracy and therapeutic targeting.

Objectives:
1. Measure serum neurofilament light chain (NfL) levels in post-COVID POTS patients compared to healthy controls.
2. Identify potential protein biomarkers for POTS using unbiased quantitative proteomics.

Methods: Serum NfL levels were quantified in 22 healthy individuals and 43 post-COVID POTS patients using Simoa® Assay Kits. For proteomics analysis, serum from 9 POTS patients and 9 controls was analyzed via high-resolution liquid chromatography-mass spectrometry (LC-MS/MS) with TMT-based quantification. Differential protein expression was assessed using bioinformatics analysis.

Results: Post-COVID POTS patients had significantly elevated age-adjusted NfL percentiles, with higher proportions in the 50th-75th and 75th-90th percentiles. NfL levels correlated with total COMPASS-31 scores. Proteomics analysis identified 31 differentially abundant proteins, primarily associated with actin filaments, immune response, and inflammation. Weighted Gene Co-Expression Network Analysis revealed key proteins strongly correlated with POTS diagnosis and symptom severity.

Conclusions: This study identifies novel candidate biomarkers for post-COVID POTS, shedding light on underlying pathophysiological mechanisms. Further validation studies are necessary to assess their diagnostic and prognostic potential, paving the way for biomarker-driven precision medicine for this often-overlooked condition.

III. Therapeutic Interventions and Outcome Measures

#1276 Revisiting Treatment Efficacy: A Case of Fibroblast Growth Factor Receptor 3 Autoantibody Associated Small Fiber Neuropathy Demonstrating a Dose-Dependent Response to Intravenous Immunoglobulin

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Introduction/Objectives: Small fiber neuropathies (SFN) are cryptogenic in 25 - 50% of cases. However, recent data suggests 44% - 55% of cryptogenic SFN is associated with specific auto-antibodies. In particular, Fibroblast Growth Factor Receptor 3 (FGFR-3) antibody is strongly associated with SFN, with a 94.7% positive predictive value. Current data on the efficacy of intravenous immunoglobulin (IVIG) on FGFR-3 positive SFN has been limited and inconsistent. We present a case of a patient with SFN with positive FGFR3 antibody serology, highlighting the distinct clinical phenotypes of SFN, the importance of antibody testing, and treatment considerations.

Methods: A retrospective chart review and review of relevant literature were performed.

Results: A 42-year-old female with a history of concussion, IBS, PCOS, L5-S1 laminectomy, migraine, DVT, positive ANA presents with chronic neuropathic symptoms dating back to 2006, initially triggered by a presumed dengue fever infection. She reported episodic facial pain, constant limb paresthesia, and autonomic features including tachycardia and dizziness. NCS/EMG was done in 2021 and 2023 on all extremities, which were normal. Lab work-up revealed FGFR3 antibody positivity. In 2020, a skin biopsy confirmed SFN with reduced epidermal nerve fiber density. IVIG therapy was initiated with 2 gm/kg with partial relief of pain, numbness, and autonomic symptoms initially, and reductions in subsequent doses (1 gm/kg monthly) led to symptom exacerbation.

Conclusions: There remains limited and conflicting data regarding the treatment of FGFR3 autoantibody-associated SFN. In our case, we saw a dose-dependent response to IVIG across neuropathic domains, including autonomic symptoms.

#1275 Comparative Evaluation of Clinical Outcome Measures in Inclusion Body Myositis Based on NT5c1A Antibody Serology Status

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Introduction: Inclusion Body Myositis (IBM) is the most common acquired muscle disease in individuals over age 40. Characterized by progressive, asymmetric muscle weakness, IBM leads to significant impairment in mobility and daily functioning. The underlying mechanisms and progression of IBM remain incompletely understood. One biomarker of interest is the presence of NT5c1A antibodies. Previous studies in small patient cohorts have shown that seropositivity for NT5c1A antibodies is associated with more severe clinical manifestations. However, larger-scale studies are needed to further characterize the impact of NT5c1A seropositivity.

Objectives: To evaluate the association between NT5c1A antibody seropositivity and how it specifically impacts functional and physical performance in a large cohort of IBM patients.

Methods: INSPIRE-IBM is an ongoing, 2-year prospective observational study with 150 patients enrolled across 13 centers. Data have been collected at Baseline, Month 6, and Month 12, with Month 18 visits currently underway. Assessments include Manual Muscle Testing (MMT), Timed Up and Go (TUG), IBMFRS, SIFA, and NIH-PROMIS Physical Function questionnaire.

Results: Currently data collection for Baseline through Month 12 visits has been completed. Month 18 visits are scheduled for completion prior to the upcoming conference. Subsequent analyses will examine the relationship between NT5c1A serostatus and longitudinal changes in both functional assessments and patient-reported measures over the 18-month period.

Conclusions: Preliminary findings suggest that NT5c1A-seropositive patients experience more rapid functional decline and greater disease burden. We hypothesize that our data will reinforce this trend, providing evidence of increased disease severity in this subgroup.

#1267 Are muscle size and quality, assessed by muscle MRI, changed in patients with Generalized Myasthenia Gravis

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Introduction: Myasthenia gravis (MG) is an auto-immune disease caused by autoantibodies targeting proteins in the neuro-muscular junction. Patients experience weakness and increased fatiguability of skeletal muscles. Continuous damage to the neuromuscular junction might mimic denervation in which muscle atrophy and fat replacement is found on MRI. In MG MRI has been used to show increased volume and increased fat replacement of eye muscles compared to healthy controls, but no study has investigated other muscles throughout the body.

Objectives: The aim of this study is to characterize whole-body muscle abnormalities in patients with Generalized Myasthenia Gravis using MRI and correlate these with validated clinical scales.

Methods: The participants with Myasthenia Gravis will be examined using 1) Whole-Body MRI, 2) clinical evaluation of weakness and fatiguability and 3) a questionnaire on activities of daily living. MRI findings will be compared to age, sex, and BMI matched healthy volunteers.

Results/Conclusions: While MG is currently thought of as a treatable, reversible disease this study could provide the first evidence of irreversible muscle damage. The study is approved by the ethics committee and the recruitment is set to start in July. Results will be presented at the meeting.

#1264 Nutritional and Swallowing Assessment in Patients with Myotonic Dystrophy Type 1: A Cross-Sectional Study

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Introduction: Myotonic dystrophy type 1 (DM1) is a multisystemic genetic disorder characterized by muscle weakness, myotonia, and progressive involvement of respiratory, metabolic, and gastrointestinal systems. Dysphagia and malnutrition are common but often under-recognized features.

Objectives: This study aimed to evaluate the nutritional status, feeding characteristics, and swallowing difficulties in a cohort of patients with DM1, to better understand their clinical needs and guide multidisciplinary management.

Methods: We analyzed data from 47 patients with genetically confirmed DM1. Parameters included BMI, the Malnutrition Universal Screening Tool (MUST), the Eating Assessment Tool (EAT-10), need for mealtime assistance, food consistency modifications, cough reflex during meals, and deambulation.

Results: The cohort had a mean age of 43.2 years and was 57% female. Malnutrition risk was identified in 17% of patients (MUST ≥ 2), with 10 individuals classified as underweight (BMI < 18.5). Swallowing difficulties were prevalent: 34% had an abnormal cough reflex during meals and 34% scored ≥3 on EAT-10, suggesting dysphagia. Only 6 patients required assistance during meals. Despite these findings, most patients consumed normal-texture foods, and only 3 required modifications. All patients maintained independent ambulation.

Conclusions: Patients with DM1 frequently present with subtle signs of dysphagia and malnutrition, despite preserved ambulation and minimal visible feeding impairments. Routine screening with tools like EAT-10 and MUST is essential to identify at-risk individuals and initiate timely dietary and rehabilitative interventions.

#1254 Dose-Finding Safety and Tolerability Study of Clenbuterol in Facioscapulohumeral Muscular Dystrophy (FSHD)

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Introduction: FSHD is a progressive muscle disorder with no FDA-approved treatments, caused by de-repression of the DUX4 gene. In Preclinical trials clenbuterol inhibited DUX4 activity in FSHD muscle cells and has anabolic effects on muscle tissue.

Objective: To determine the optimal dose of clenbuterol that is safe, well-tolerated, reduces DUX4 activity, and increases muscle volume in FSHD patients.

Methods: This 6-month, non-randomized, open-label trial, part of the NIH Wellstone Study, involves 30 genetically confirmed FSHD patients at three sites. Participants receive escalating doses of clenbuterol (20 mcg, 40 mcg, 60 mcg) orally twice daily. Primary endpoints are safety and tolerability. Secondary endpoints include changes in MRI, molecular markers, and functional biomarkers.

Expected Results: Identify the maximum tolerable dose, potential side effects, and preliminary efficacy signs.

Conclusions This study will help define the maximum tolerated dose of clenbuterol in FSHD and provide early insights into its therapeutic potential, informing the design of future randomized trials.

#1253 Altered corticospinal excitability in Myotonic Dystrophy Type 1: a neural mechanism of fatigue?

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Introduction: Fatigue is debilitating in adults with Myotonic Dystrophy Type 1 (DM1), yet neural mechanisms of fatigue remain poorly understood. This knowledge gap limits development of targeted interventions to reduce fatigue.

Objectives: Compare indices of corticospinal excitability in adults with DM1 versus healthy controls and explore its relationship with perceived fatigue and fatigability.

Methods: Patients with DM1 and age/sex-matched healthy controls (HCs) are enrolled. Participants complete fatigue-related patient reported outcomes and fatigability test. Transcranial magnetic stimulation is delivered via double cone coil over motor cortex with motor evoked potentials (MEPs) recorded from vastus lateralis. MEPs elicited at 130% Active Motor Threshold for 10%, 30%, 50%, 70% maximum voluntary isometric contraction (MVIC) in non-fatigued state. All measurements repeated after standardized fatiguing protocol. Due to currently small sample size, data analyzed via descriptive statistics, and patterns of MEP modulation visually inspected for relationship with fatigue measures.

Results: Three adults with DM1 (age range 39-47, 2F/1M) and one healthy control (45F) have completed the study. At all percent MVICs in non-fatigued and fatigued state, DM1 MEPs were lower than HCs. Also, DM1 MEPs exhibited altered modulation at increasing levels of effort compared to HCs. Combined effect of low MEPs and altered modulation may impact fatigue.

Conclusions: Preliminary data suggest that adults with DM1 may exhibit reduced magnitude and altered modulation of corticospinal excitability compared to a healthy control. These differences could be relevant to fatigue in DM1, but conclusions remain tentative given limited sample size. Enrollment is ongoing; updated results will be presented.

#1251 Whole-body Electrical Muscle Stimulation Exercise as an Alternative Exercise Paradigm Promoting Functional Improvement in Adults with Myasthenia Gravis

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Introduction: Patients with Myasthenia Gravis (MG) experience fatigability and muscle weakness that impact physical function. Exercise can improve physical function in MG, but traditional strengthening and aerobic exercise can be difficult for this population to tolerate.

Objectives: To investigate the effects of whole-body electrical muscle stimulation plus exercise (WB-EMS Exercise) on measures of fatigue, function, and NMJ transmission in adults with MG.

Methods: Enrolled participants completed a 4-week exercise intervention using a commercially available WB-EMS system (10-12 exercises performed in 20 minutes at mild to moderate intensity, 2x/week; stimulation levels were tailored to individual responses). Pre-test and post-test measures were taken 2-4 days before and after the intervention period using the following tests: Fatigue Severity Scale (FSS), Six-minute Walk Test (6MWT), Arm Movement Test (AMT), Quantitative Myasthenia Gravis (QMG), and Single Fiber Electromyography of the vastus lateralis (SFEMG). Paired t-tests were used to analyze differences between pre-test and post-test measures.

Results: Six participants have enrolled and completed the study (age range 21-77, 3M/3F). Trends toward improvement were observed in perceived fatigue (FSS), arm endurance (AMT), and neuromuscular junction transmission (SFEMG). Statistically significant increases occurred in walking endurance (6MWT). QMG scores were stable but may have been confounded by testing order differences between pre-test and post-test.

Conclusions: WB-EMS Exercise may modify fatigue and NMJ function in adults with MG and improve physical function. Results suggest that WB-EMS Exercise is an effective and tolerable alternative to traditional exercise. Recruitment and data collection are ongoing. Updated results will be presented.

#1249 COMBINED USE OF ZILUCOPLAN AND RITUXIMAB FOR ACETYLCHOLINE RECEPTOR ANTIBODY POSITIVE (ACHR+) GENERALIZED MYASTHENIA GRAVIS

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Introduction/Objectives: Zilucoplan was developed as therapy for treatment refractory cases of AChR+ generalized myasthenia gravis. There is no data on combined use of zilucoplan (a macrocyclic peptide C5 inhibitor) and rituximab (chimeric anti-CD20 monoclonal antibody). We report a case of refractory generalized myasthenia gravis in which zilucoplan and rituximab were used in combination to better manage myasthenia symptoms.

Methods: CASE REPORT

Results: A 23-year-old woman with AChR+ myasthenia gravis since age 17 status post thymectomy was on eculizumab every 2 weeks with breakthrough symptoms within 5 days of her infusions. Her initial AChR antibody titer was 475nmol/L. She was trialed on efgartigimod for 2 cycles, but developed myasthenia exacerbations that were responsive to plasma exchange. She received one cycle of rituximab 1g IV x 2. AChR titers dropped to 263.8 nmol/L. She remained symptomatic (MG-ADL > 6), restarted eculizumab with prednisone and mycophenolate mofetil. After 3 months, she transitioned to ravulizumab; 6 weeks later, she had a myasthenia exacerbation that responded to plasma exchange. She resumed eculizumab, continued to have breakthrough symptoms, and 2 months later was started on zilucoplan. However, she continued with intermittent breakthrough weakness, requiring plasma exchange. Rituximab 1g IV x 2 every 6 months was initiated, mycophenolate was stopped, and prednisone was reduced. She had less myasthenia symptom fluctuation and improvement of MG-ADL to 2.

Conclusions: This case demonstrates combination therapy of a C5 peptide inhibitor and a CD20 monoclonal antibody as a possible treatment strategy to better manage the clinical symptoms of refractory myasthenia gravis

#1248 Masseter Muscle Volume is Associated with Disruptions in Cerebral White Matter Integrity and Motor Endpoints in Myotonic Dystrophy Type 2

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Introduction: Myotonic dystrophy type 2 (DM2) affects both muscle and brain but collecting concurrent MRIs is not always feasible.

Objectives: To examine masseter volume (MV) as a proxy of disease severity of brain and, opportunistically, muscle in DM2.

Methods: From T1-MPRAGE brain MRIs, bilateral MV was manually segmented. MV was divided by lean body mass (MV_{LBM}) estimated using the James formula. Diffusion tensor imaging parameters (fractional anisotropy [FA], and radial diffusivity [RD]) were measured as indicators of cerebral white matter (WM) integrity. FA is an index (0-1) of non-uniform movement of water molecules (higher values represent well-organized WM), while RD represents diffusion rates (lower values represent healthier WM). MV and MV_{LBM} between DM2 and controls were compared using linear regression. FA, RD and motor endpoints were correlated with MV_{LBM} (Pearson correlation, r); significant p-values at an FDR rate of 5%.

Results: Compared to controls (n=24, age 60±8yrs, 63% female), DM2 participants (n=35, 58±8yrs and 51% female) showed smaller MV (mean difference, 3.79cm^3 p-val=0.037) and MV_{LBM} (0.082cm^3/kg, p-val=0.0032). These differences remained significant after age and sex adjustments (MV p-val=0.0024, MV_{LBM} p-val=0.0009). MV_{LBM} was associated with lower FA (r=0.39, p-val=0.021), higher RD (r=-0.37, p-val=0.027), short physical performance battery (SPPB; r=0.51, p-val=0.0019), 6-minute walk test (6MWT; r=0.50, p-val=0.003), step test (r=0.48, p-val=0.007), grip strength (r=0.42, p-val=0.014), and pinch test (r=0.54, p-val=0.001). The SPPB, 6MWT, step test, and pinch test remained associated with MV_{LBM} after adjusting for age.

Conclusions: Our data suggests that masseter size is reduced in DM2, and this measure correlates with white matter pathology and motor function.

Funding: This study was supported by the NINDS Career Development Award (K23 NS125110) to AP. Additional support was provided by the Myotonic Dystrophy Foundation to DAMF.

#1242 Impact of Exon-Skipping Therapy in Ambulatory and Non-Ambulatory Duchenne Muscular Dystrophy: Real-World Evidence from a Specialty Center

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Introduction: Duchenne muscular dystrophy (DMD) is a leading cause of progressive muscle weakness in males, typically presenting in early childhood. Without treatment, boys often lose ambulation between ages 9 and 12 and may develop cardiac and respiratory complications, resulting in early mortality. Mutations in the dystrophin gene between exons 45 and 53 account for nearly half of DMD cases. Exon-skipping therapies can restore the reading frame, enabling production of a partially functional dystrophin protein. Three exon-skipping drugs—eteplirsen, golodirsen, and casimersen—are FDA-approved in the United States.

Objectives: This study aimed to retrospectively evaluate multisystem outcomes—motor, pulmonary, and cardiac—in patients with DMD amenable to exon 45, 51, or 53 skipping, treated at Stanford Children's Hospital, and to compare outcomes to natural history data.

Methods: A retrospective chart review was conducted on 21 patients with genetically confirmed DMD amenable to exon 45, 51, or 53 skipping. Eleven received eteplirsen, six received golodirsen, and four received casimersen. Clinical data including ambulatory status, 10-meter walk time, forced vital capacity (FVC), and cardiac ejection fraction were collected and analyzed over 5 to 10 years. Outcomes were compared with published natural history cohorts.

Results: Fourteen patients were ambulatory at treatment initiation; eight remained ambulant at follow-up. Six lost ambulation between ages 10 and 13, suggesting a delayed decline. Pulmonary function was preserved or declined more slowly; about half maintained stable FVC. Cardiac function remained stable, with 48% maintaining ejection fraction >55%.

Conclusions: This real-world cohort supports previous findings that exon-skipping therapies slow functional decline and demonstrate sustained benefit over long-term treatment.

#1237 Assessment of perceived physical fatigability in spinal muscular atrophy using the SMA EFFORT

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Introduction: Fatigability is a persistent feature of SMA not captured using existing patient-reported measures.[1] Attempts to quantify fatigability lack specificity and standardization.[2] With the advent of disease-modifying therapies (DMTs) and anticipated availability of adjuvant treatments with distinct biological targets, an improved method to capture experienced fatigability is needed.[3]

Objectives: Assess experienced fatigability using the revised SMA EFFORT in a diverse cohort of individuals with SMA.

Methods: Participants (N=88) with SMA (≥12 years) completed the SMA EFFORT and self-reported clinical characteristics. The scale asks participants to rate their fatigability (5-point Likert scale) while performing specific activities in the past 30 days. Overall and subscale fatigability scores were generated. Regression examined associations with current function and treatment.

Results: Mean age was 36.9 years (range: 13-78) and 53% were female. Participants were non-sitters (29.5%), sitters (41.0%) and walkers (29.5%). More activities were endorsed by walkers (21.0±2.7), followed by sitters (15.8±3.3), and non-sitters (10.9±3.4). DMT was reported by 81/88 individuals, with three reporting dual treatment. Non-sitters reported greater overall fatigability than sitters and walkers, $p<.0001$. Walkers reported greater fatigability in the mobility subscale, $p<.0001$, while non-sitters had greater fatigability in the ADL and postural control subscale(s), $p<.01$. Participants on risdiplam (54.5%) reported greater fatigability than those on nusinersen (34.1%), $p=0.0185$, without controlling for additional factors.

Conclusions: Individuals with SMA experience fatigability during daily activity that is captured using the SMA EFFORT. Ongoing work will further validate the scale and evaluate its sensitivity to change, establishing it as a valuable tool for clinical management and research.

Acknowledgements: This work was supported by the Neuromuscular Study Group and through the Cure SMA PNCRN infrastructure grant.

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#1236 Exploring the assessment of muscle volume as a potential biomarker for muscle targeted therapies in spinal muscular atrophy (SMA)

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Introduction: Myostatin inhibition is a promising therapy and has been shown to increase muscle mass and function in pre-clinical SMA models[1] and improve function in non-ambulatory children with SMA[2]. While muscle volume[3] and quality has been studied in SMA[4,5], its association with function in ambulatory SMA is not well described.

Objectives: Explore the association of muscle volume with leg strength and function in ambulatory SMA.

Methods: Muscle resonance imaging (MRI) assessed lower extremity muscle volume, using 5-mm-thick axial slices with sliceOmatic imaging software. The six-minute walk test distance in meters (6MWT), timed 10-meter walk/run test (10MWR) and 30-second sit to stand (30STS) assessed function. Hand-held dynamometry assessed strength of knee extensors/flexors and ankle plantarflexors/dorsiflexors.

Results: Twenty-five individuals, mean age of 20.21 (9.13) years were included. The group was mostly female (64%), with treatment duration averaging 7.52 years (2.58). Though the group was ambulatory, a range of function was represented, with a median 6MWT distance of 400m(33-682) and 10MWR time of 7.18 seconds (3.20-21.28). Leg muscle volume was positively associated with 6MWT ($r=.688$, $p<.001$) and 30STS ($r=.492$, $p=.015$) and inversely associated with 10MWR ($r=-.605$, $p=.001$). There were no associations between leg muscle volume and strength. ($p>.05$).

Conclusions: Leg muscle volume is associated with function in treated ambulatory SMA and may serve as a useful biomarker for muscle targeted therapies. This work provides foundational knowledge about muscle volume necessary to better understand the impact of myostatin-inhibitors. Future work will study muscle volume's sensitivity to change over time and response to therapies.

Acknowledgements: This work was supported by an investigator-initiated study sponsored by Genentech (ML44201).

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#1227 Motor Outcomes to Validate Evaluations in Pediatric Facioscapulohumeral muscular dystrophy (MOVE Peds): Protocol for an observational study

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Introduction: FSHD severity and its impact on function are often more severe in children, and measurement tools must account for the effects of growth and maturation on motor function. Cross sectional studies have suggested an association between earlier onset and greater clinical severity. Prospective studies in early-onset FSHD have been limited by small numbers of sites and low ability to recruit and follow patients. While the adult FSHD field has coalesced around outcome measures (FSHD-COM, RWS, and qMRI), academic and industry experts agree there is an urgent need for data in pediatric FSHD.

Objectives: The goal of this study is to hasten therapeutic development by validating outcomes and refining trial strategies for pediatric-onset FSHD, which is defined as onset of symptoms before the age of 18 years and includes approximately one fifth to a third of individuals with FSHD.

Methods: This prospective observational study will enroll 80 symptomatic, genetically confirmed pediatric FSHD participants (at least half meeting criteria for early-onset: facial weakness before 5, shoulder weakness before 10) over 24 months. Visits will occur every 6 months and collect history, exam, patient reported outcomes, functional motor performance (FSHD COM Peds, strength, and respiratory parameters), reachable workspace, and whole-body MRI.

Results: We hypothesize that baseline features in qMRI will predict 24-month changes in FSHD-COM Peds or RWS. Funding has been provided by the NINDS, sites are being activated, and enrollment is has begun!

Conclusion: Validating measures in children with FSHD will improve trial readiness. Outcomes that can span the lifetime would offer advantages for clinical trials, enable longitudinal studies, and support effective health monitoring in integrated lifespan care models.

Funders: National Institute for Neurological Disorders and Stroke

#1226 Motor Outcomes to Validate Evaluations in Facioscapulohumeral muscular dystrophy (MOVE FSHD): Interim Baseline Data and Potential Predictors for FSHD

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Introduction: The MOVE FSHD study aims to determine the predictive value of clinical and motor assessments, patient-reported outcomes, and imaging and tissue biomarkers on disease progression in FSHD.

Objective: This prospective observational study will evaluate 450 FSHD participants over 24-months with 200 participating in the MOVE+ sub-study.

Methods: Visits include physical examination, patient-reported outcomes, FSHD history, strength, timed functional tests (TFTs), and spirometry. Sub-study participants have additional biomarkers collected, including reachable workspace at each visit, whole-body MRI at Baseline and 12-months, optional muscle biopsy occurring at Baseline and (n=40) at 4-months, and optional wearable device every 6-months.

Results: The MOVE FSHD study has enrolled >400 participants across 18 international sites: 100 are enrolled in the MOVE+ sub-study, ~30 are pediatric, and ~30 are non-ambulatory. TFTs, such as the 10-meter walk run (10mwr) and Timed Up and Go (TUG), correlate well with disease severity (>0.6), change from Baseline in 12-24-months. The current abilities scale (CAS), a patient-reported outcome, also has a strong correlation to disease severity and strength (>0.8), as well as a moderate correlation to function (>0.5). For every increase of 1 in the CAS, there is a change of .9 seconds in the 10mwr and can be used to help indicate clinically meaningful change over time.

Conclusions: The MOVE FSHD study has improved our understanding of FSHD, impacted direct patient care, refined inclusion/exclusion criteria for clinical trials, as well as identified outcomes and biomarkers for FSHD. These outcomes can be used to indicate a clinically meaningful change and predict shifts in other measures.

Funders: Grants from FSHD Society, Friends of FSH Research, FSHD Canada, Avidity Biosciences, Dyne Therapeutics, and Hoffman-La Roche.

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#1219 Developmental Assessment Using the DP4 in Children with SMA Type 1

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Introduction: Patients with Spinal Muscular Atrophy (SMA) have historically been described as having normal to above average intelligence. In the era of disease-modifying therapies, it has become apparent that a subset of patients have significant neurocognitive delays that are not adequately being assessed or managed.

Objectives: To examine performance across multiple developmental areas in children with SMA type 1 using the Developmental Profile 4 (DP4) assessment tool.

Methods: The DP4 Parent Interview was administered to pediatric patients with SMA type 1 during their routine neuromuscular appointments. Pertinent clinical information was obtained via chart review. Data was analyzed using descriptive statistics.

Results: Eight patients with SMA type 1 were evaluated: 3 were female, 6 received gene therapy, 3 were symptomatic at the time of dosing, 4 started add-on therapies after gene therapy, and 1 had a comorbid genetic neurodevelopmental disorder. In the physical domain, 2 were below average and 6 were delayed. In the adaptive behavioral domain, 2 were average, 2 below average, and 4 delayed. In the social-emotional domain, 3 were average, 4 below average, and 1 delayed. In the cognitive and communication domain, 2 were above average, 4 average, and 2 delayed.

Conclusions: Delays in physical, adaptive behavioral, and social-emotional domains were identified in this cohort using the DP4, supporting the need for further studies on developmental outcomes and comprehensive developmental monitoring in SMA. We plan to expand screening via DP4 to all SMA patients and correlate with SMN2 copy number.

#1217 Enhancing Bulbar Assessment in Spinal Muscular Atrophy (SMA): A Rasch Analysis of the International Bulbar Assessment Tool (iBAT) Pilot Study

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Introduction: Individuals with SMA experience progressive bulbar weakness including deficits in swallowing, voice and articulation. Disease-modifying therapies are effective; however, standardized/validated bulbar outcomes evaluating multiple domains are unavailable. A multidisciplinary team developed a clinical bulbar function outcome, without specialized equipment/training, promoting international and interprofessional administration. Consensus was reached on a 95-item bank.

Objectives: To assess psychometric properties of iBAT to select bulbar items suitable to monitor disease, support management, and evaluate treatment.

Methods: 235 responses were assessed using Rasch analysis to evaluate item thresholds, item/person fit, reliability and targeting.

Results: iBAT was completed by 130 individuals (55%) and 105 caregivers (45%) with varying phenotypes and oral intake. 80 items were evaluated, yet only 15 (19%) had ordered thresholds, reflecting the need to simplify the response scale. Six items (8%) indicated misfitting responses and may not exhibit the intended bulbar construct. Overlap in item locations supports the need for item reduction. Reasonable item fit (mean=0.067; SD 1.97), good person fit (mean=0.159; SD 1.44), and reliability was good (Person Separation Index=0.93). For targeting, the item distribution revealed over measuring of weaker individuals and needing additional items for stronger individuals.

Conclusions: The iBAT may be a useful measure of bulbar function in all individuals with SMA, and demonstrates encouraging psychometric properties; however, work is necessary to refine responses and address item fit/redundancy to enhance measurement precision/targeting. This will promote advancement of assessing bulbar function in SMA internationally by health professionals, without specialized equipment/training, and lay a foundation towards providing evidence-based care.

Acknowledgements: We gratefully thank the study participants and their families for their willingness to participate. We thank the international SMA Consortium (PNCR-USA, SMA REACH-UK, SMA Telethon-Italy) and all clinicians who participated in the Bulbar Function in SMA Workshop. We wish to thank Cure SMA and the Industry Collaboration for the funding that supported this project.

#1209 Inclusion Body Myositis Treatment with Celution Processed Adipose Derived Regenerative Cells

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Introduction: IBM is a progressive, debilitating disease leading to proximal and distal muscle weakness, most prominently in the quadriceps and finger flexors. The Celution 800/CRS System is a closed, automated system intended to digest adipose tissue to further extract, wash, and concentrate stromal stem cells intended for autologous reimplantation in a real-time bedside manner.

Objectives: The objective of this study is to assess in Inclusion Body Myositis (IBM) the safety of an autologous graft consisting of adipose-derived regenerative cells (ADRCs) derived from the Celution 800/CRS System.

Methods: Nine IBM subjects were randomized 2:1 in blocks of 3 to late (Part 1) versus early (Part 2) ADRC autologous graft injections. We injected 30 million cells divided between 8 injections unilaterally: 2 sites in the flexor digitorum profundus and 6 sites in the quadriceps. We followed the subjects every 3-6 months for two years after ADRC injections for safety and efficacy measures. Subjects were considered to be treatment responders if they experienced no more than 2-point drop in IBMFRS score at 12 months compared to baseline.

Results: Subjects included 5 female and 4 male IBM patients with a mean age of 66.55 (range 61-74). The study-related adverse events have been so far limited to transient mild to moderate side effects. Five of nine subjects were determined to be treatment responders at 12 months post treatment according to IBMFRS scores.

Conclusions: ADRC intramuscular injections are safe and well-tolerated in IBM. While pilot data looks promising, a future study is needed to determine efficacy.

#1204 Combining complement inhibition and antibody reduction in refractory AChR generalized myasthenia gravis (gMG)

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Introduction: Complement inhibition, B-cell depletion and FcRn blockade may each partially benefit patients with refractory AChR gMG. To achieve remission or minimal manifestations, combining complement inhibition with either B-cell depletion or FcRn blockade provides a strategy to simultaneously target two aspects of MG pathophysiology: complement-mediated destruction of the post-synaptic membrane architecture and interaction of pathogenic antibodies with ACh receptors.

Objectives: To describe clinical outcomes and safety following combined therapy with a complement inhibitor and either rituximab or efgartigimod in 5 patients with treatment-refractory AChR gMG.

Methods: We identified 5 patients treated with this strategy by three physicians in outpatient neuromuscular clinics. We assessed gMG symptoms before and during combination treatment, using patient-reported (MG-ADL, MG-QOL15), composite (MGC) and objective (MG-MMT) scales.

Results: Clinical improvements were seen in 3 patients (Pt#1: eculizumab+rituximab, Pt#2: ravulizumab+rituximab, Pt#3: zilucoplan+efgartigimod). No definite changes were seen in Pt#4 (ravulizumab+rituximab). Pt#5 initially improved but later worsened (on eculizumab+rituximab, then zilucoplan+rituximab, then zilucoplan+efgartigimod). Responders had early-onset MG (ages 24, 36, 37 at onset) and longer disease duration (17, 30 and 14 years respectively) compared to nonresponders (56, 79 at onset; 6, 1.5 years disease duration respectively). All patients concomitantly received azathioprine, mycophenolate or cyclosporine; 4 also received prednisone. Pt#2 and Pt#3 developed localized herpes zoster infections. Pt#5 had a mild COVID infection.

Conclusions: Combination of complement inhibition with either B-cell depletion or FcRn blockade may improve symptom control in some patients with treatment-refractory myasthenia. Additional studies are needed to better understand the safety and efficacy of this approach.

#1201 Utility of Vagus and Phrenic Nerve Ultrasound in Patients with Motor Neuron Disease as a Potential Predictor of Disease Progression

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Introduction: High-resolution ultrasound is a valuable non-invasive diagnostic tool in neuromuscular disorders including motor neuron disease (MND). The vagus nerve (VN) and phrenic nerve (PN) are affected in most MND patients during the disease; however, limited studies assess the utility of ultrasound of these nerves to monitor disease progression.

Objectives: Evaluate sonographic findings of the VN and PN in MND patients and monitor nerve changes over time.

Methods: In this prospective study, patients with amyotrophic lateral sclerosis (ALS), primary lateral sclerosis (PLS), and age-matched controls were enrolled. Demographics, VN and PN cross-sectional area (CSA) bilaterally, and clinical variables were recorded. ALS and PLS patients were followed every 3–6 months for up to 24 months to monitor clinical and ultrasound changes. A linear mixed-effects model was used to evaluate changes over time.

Results: A total of 133 subjects were enrolled (ALS: 63, PLS: 11, Controls: 59). At baseline, VN CSA did not differ significantly between ALS (2.125 mm^2), PLS (2.165 mm^2), and controls (2.25 mm^2). However, PN CSA was significantly smaller in ALS (0.44 mm^2) and PLS (0.425 mm^2) than in controls (0.52 mm^2, $p = 0.004$). In ALS patients, VN and PN CSAs significantly declined over time, with average reductions of 0.130 mm^2 ($p = 0.002$) and 0.019 mm^2 ($p = 0.037$) per visit, respectively. At baseline, PN CSA did not differ significantly between patients using non-invasive ventilation (NIV) and those not using NIV ($p = 0.052$)

Conclusions: VN and PN ultrasound may serve as biomarkers to monitor disease progression in MND. Enrollment and data collection are ongoing. This study may help to define diagnostic sonographic criteria and improve MND subtype classification.

#1181 Measuring lower limb movement with Syde® in patients with Facioscapulohumeral muscular dystrophy (FSHD): Analytical validation in a controlled environment

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Introduction: Facioscapulohumeral muscular dystrophy (FSHD) is a slowly progressing neuromuscular disease that causes progressive muscle loss in the facial, shoulder, and upper-arm musculature, with lower limb and pelvic affection typically appearing at later stages. Approximately 20% of patients will require a wheelchair. There are no curative treatment options for FSHD, but multiple trials are ongoing. Currently used endpoints in trials targeting FSHD are limited by poor sensitivity to change in clinical function, resulting in long trials required to show an effect. A solution to this is the development of new, objective, and sensitive endpoints from Digital Health Technologies (DHT). Syde® is a wearable DHT that measures the 3D-trajectory of the limbs and produces digital variables. The Syde®-variable SV95C is already EMA-approved as a primary endpoint for Duchenne Muscular Dystrophy.

Objectives: We aim to validate Syde's® efficacy in measuring lower limb movements in patients with FSHD.

Methods: Seventeen participants with FSHD completed daily living activities while equipped with the Syde® in a controlled environment using gold-standard optical motion cameras as control.

Results: Syde® had a stride detection precision of 99.3% and recall of 98.3%. Stride length mean error was 0.6cm, and standard deviation absolute error was 2.9cm. Stride velocity mean error was 0.5cm/s, and stride velocity standard deviation absolute error was 3.1cm/s. Performance was independent of clinical severity, age, walking aids, height, and weight.

Conclusions: These results show that Syde® has a great efficacy in measuring lower limb movements in patients with FSHD and warrants further validation of Syde® in FSHD.

#1177 Retrospective analysis of efficacy and outcomes of daily versus alternate day plasma exchange in myasthenic crisis: A single center experience

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Introduction: Myasthenia Gravis (MG) is an autoimmune disease characterized by fatigable muscle weakness. Manifest myasthenic crisis (MC) is defined a severe myasthenic weakness requiring intubation or noninasive respiratory support, and impending MC describes a rapid worsening of MG that could lead to a crisis in days-weeks. Plasmapheresis is first-line therapy for myasthenic patients with severe weakness.(2) There is no consensus on the schedule, number of plasma exchanges (PLEX) in myasthenic crisis or impending myasthenic crisis. One 2005 randomized clinical trial of 33 patients of daily versus alternate day plasmapheresis in severe MG found no superiority of one over the other in terms of disease improvement and complication occurrence.

Objectives: To clarify outcomes of daily versus every other day or greater PLEX in patients with severe myasthenic weakness.

Methods: This is an observational retrospective cohort study utilizing chart review of inpatients at the Strong Memorial Hospital in Rochester, NY admitted for impending or manifest myasthenic crisis. Primary outcome measures were total duration of hospital stay and MG-ADL score at outpatient follow up. Demographic information, clinical information including disease duration, thymoma status and existing MG treatment regimens, and in-hospital complications were also assessed. Daily PLEX was defined as at least 3 consecutive PLEX, and qOD or greater PLEX was defined as at least 3 non-consecutive PLEX. The two groups were compared using chi square test when parametric variables were evaluated. Student t-test was used to compare numerical variables. In this study a statistically significant difference was considered if the p value was < 0.05.

Results: A total of 30 patients were evaluated. Average age at time of PLEX was 58.4 years. 24 patients were AchR Ab (+), 2 MuSK Ab (+), 1 LRP4 Ab (+) and 3 patients were seronegative. 16 patients had daily PLEX and 15 patients had qOD or greater PLEX. 7 patients in total were intubated, 4 in the daily PLEX group and 3 in the qOD or greater PLEX group. 1 patient receiving qOD PLEX died. Mean hospital length of stay for the daily PLEX group was 12.5 days, and 14.1 days for the qOD or greater PLEX group, and this difference was not statistically significant ($p=0.65$). The mean MG-ADL score for the daily PLEX group was 5.8, and the mean MG-ADL score for the qOD or greater PLEX group was 4.9 ($p=0.85$).

Conclusions: In this small, retrospective observational cohort, no statistically significant differences in length of hospital stays or MG-ADL at outpatient follow up were seen between patients receiving daily or qOD or greater PLEX for impending or manifest myasthenic crisis. Larger, prospective studies are needed to clarify optimal PLEX regimens for patients with severe myasthenia gravis.

#1166 Identification and treatment of neurodevelopmental and mental disorders in boys and adults with Duchenne muscular dystrophy: a cohort study

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Introduction: Over the last few years there has been increasing attention to the involvement of central nervous system in Duchenne muscular dystrophy.

Objectives: The aim of this study was to assess the spectrum of neurodevelopmental and mental disorders and possible required intervention in our cohort of 264 boys and adults with Duchenne muscular dystrophy.

Methods: We retrospectively analyzed clinical notes and psychological assessments, including routinely performed cognitive tests and clinical observations. Intelligence quotients and site of mutations were also noted.

Results: 103/264 individuals (39%) had symptoms compatible with one of the following diagnosis: Attention deficit and Hyperactivity disorder (ADHD) (n=26), Autism spectrum disorder (ASD) (n=11), Depressive mood/Disruptive mood dysregulation disorder (n=27), Anxiety disorder (n=17), Obsessive-compulsive disorder (n=2), Psychosis Risk Syndrome (n=7), thirteen had a more complex phenotype. ADHD and ASD were more frequent in infancy, emotional dysregulation during early adolescence and psychosis and more severe phobias in older boys and adults. The risk of developing these disorders did not increase with the concomitant involvement of the dystrophin isoforms Dp140 and Dp71. Pharmacological treatment was suggested for 48 individuals but was started only in 24, as it was refused by the remaining 24 families.

Conclusions: Our findings confirm that neurodevelopmental and mental disorders are common in Duchenne and are likely to have a multifactorial nature. These findings support the need for disease specific assessments, and the need to increase awareness of the possible behavioral and social difficulties among families and health care professionals.

#1159 Evolution of pharmacological management for non-dystrophic myotonias (NDM): a UK cohort study (1998–2024)

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Introduction: Non-dystrophic myotonias (NDM) are skeletal muscle channelopathies caused by ion channel dysfunction, including myotonia congenita (MC), sodium channel myotonia (SCM), and paramyotonia congenita (PMC). They are characterised by muscle stiffness due to myotonia. Though incurable, symptoms are treatable pharmacologically.

Objectives: To analyse efficacy of pharmacological management in NDM.

Methods: We analysed genetically confirmed adult NDM patients referred to the UK Highly Specialised Service (HSS) between 1998-2024 from our skeletal muscle channelopathy cohort database.

Results: Of 96 adults (CLCN1: 54.2%; SCN4A: 45.8%; female: 36.5%; median age: 51), 93.8% initiated medications. Patients declined treatments because of mild symptoms, contraindications and side effect concerns. Mexiletine was first-line in 75.5%, Lamotrigine second-line (55.2%). At follow-up, 67.4% remained on medications (Mexiletine: 53.9%; Lamotrigine: 34.9%). Medication changes were common (83.4% switched ≤3 times; max 9), driven by inefficacy (45.0%) and side effects (33.5.0%; of which 38.3% were GI-related). Males switched mainly due to inefficacy (55.7%), females due to side effects (42.3%). Myotonia symptoms persisted in 48.3% of medication users at last visit, more in females (54.3%) than males (37.7%), and in CLCN1 (50.0%) than in SCN4A (41.5%). 36% of patients prescribed Mexiletine reached the maximum recommended dose of 600mg; among them 85% were men and 15% were female. Most patients required doses of Mexiletine between 400mg (19.7%) and 600mg (21.1%) for symptom control.

Conclusions: Drug therapy is common in NDM, but myotonia symptoms often persist, leading to multiple medication changes. Females remained more symptomatic and less likely to reach higher mexiletine doses. These findings highlight the need for more effective, targeted treatments.

#1358 Female carriers of BMD and DMD variants exhibit elevated levels of muscle injury proteins and progression of muscle loss is predicted by ART3 levels in plasma

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Introduction/Objectives: Duchenne (DMD) and Becker muscular dystrophy (BMD) primarily affect men due to pathogenic variants in the dystrophin (DMD) gene on the X-chromosome. However, women carrying DMD gene variants may also develop varying degrees of muscular and cardiac involvement. Comprehensive proteomic profiling in this population remains limited. This study identified proteomic biomarkers associated with muscle involvement, compared biomarkers between DMD/BMD carriers and healthy controls, and explore their correlation with disease severity and progression.

Methods: Plasma from 30 DMD and 16 BMD carriers and 21 age-matched healthy controls was analyzed using the SOMAscan proteomics platform. A subset had a 6.5-year follow-up (DMD: 12, BMD: 9). Thigh muscle fat fraction (FF, n=44) was assessed to examine correlations with proteomic biomarkers.

Results: Compared to controls, carriers exhibited elevated plasma proteins indicating ongoing muscle injury, independent of clinical symptoms. Notably increases were in creatine kinase muscle type (CKM) and Troponin I type 2 (TNNI2), significantly elevated in DMD/BMD carriers, whereas ecto-ADP-ribosyltransferase 3 (ART3) was decreased. CKM and TNNI2 were significantly higher in carriers, particularly variants predicted to confer DMD. Muscle FF >15% were linked to elevated markers of muscle injury, dysregulated lipid storage and inflammation, and lower ART3—previously linked to muscle function in dystrophinopathy. Baseline ART3 negatively correlated with quadriceps fat fraction increase at follow-up ($r=-0.786$, $p<0.0001$), suggesting potential as a predictive biomarker.

Conclusions: Women carrying DMD gene variants exhibit proteomic evidence of muscle injury, even without clinical symptoms. Increased fat replacement correlated with muscle injury biomarkers; lower baseline ART3 predicted disease progression.

#1144 Testing cognitive development in weak infants with Spinal Muscular Atrophy: insights and challenges

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Introduction: Since the introduction of disease-modifying therapies for individuals with Spinal Muscular Atrophy (SMA), there has been growing interest in exploring potential cognitive and neurodevelopmental comorbidities. One challenge in evaluating cognitive and developmental delays in children with SMA type I is that commonly used assessment tools often include materials and items unsuitable for frail infants.

Objectives: The purpose of this study was to make adjustments to widely used developmental scales to better suit children with SMA. This was achieved by adapting both the materials and the testing environment.

Methods: A professional 3D printer and lightweight 3D printed textures were utilized to modify some materials by reducing their weight while preserving the original shape and color. Additionally, a more appropriate setting was standardized to administer the tasks, ensuring correct head and trunk posture, positioning materials suitably for each child to optimize visual scanning, and testing the child at rest prior to the motor assessment to minimize fatigue.

Results: Both the original test and the lighter version were administered to 11 children with SMA type I. Performance on the tasks, fatigability, and time-dependent items were evaluated. Children with SMA and severe motor impairment scored better using the lightweight developmental scale compared to the standard protocol.

Conclusions: These findings indicate that modifying assessment tools, including weight reduction and postural adjustments, may provide more reliable data when assessing cognitive abilities in frail children with SMA, where low scores may partly reflect difficulties with standard test materials and procedures. Larger, collaborative studies are needed to identify the most suitable tools for evaluating these vulnerable infants with SMA.

#1140 Longitudinal assessment of 4-year HFMSE changes in SMA II and III patients treated with nusinersen

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Introduction: The advent of disease-modifying therapies (DMTs) has dramatically changed the progression of SMA, not only in type I infants, with increased survival and often achievement of sitting, but also in types II and III.

Objectives: The aim of this international retrospective study was to assess 4-year change using the Hammersmith Functional Motor Scale Expanded (HFMSE) in individuals with type II and III spinal muscular atrophy (SMA) treated with nusinersen and to establish predictors of HFMSE changes.

Methods: Individuals with type II or III SMA, and at least 4 years of nusinersen-only treatment were included. All were assessed using the HFMSE. Age at baseline, sex, motor function, SMN2 copy number, and age of onset were also retrospectively collected. Linear mixed effect models were used to calculate yearly changes and trajectory predictors.

Results: We included 73 individuals with SMA type II (mean age 8.58 years, SD 7.91, IQR 3.04-10.70) and 111 type III (mean age 7.91 years, SD 17.83, IQR 8.15-34.42). Over 4 years, mean changes were +4.18 (95% CI: 2.85–5.50) for SMA II and +1.08 (95% CI: 0.12–2.04) for SMA III. Age (SMA II: −0.34 \[−0.51 to −0.17]; SMA III: −0.13 \[−0.20 to −0.06], p<0.001) and baseline HFMSE (SMA II: 1.02 \[0.70–1.34]; SMA III: 0.79 \[0.71–0.87], p<0.001) were the strongest predictors of progression, with younger age and higher baseline scores associated with better outcomes. Functional status was only predictive for type III (6.96\[4.26–9.66]).

Conclusions: Our results confirm that, given a follow up of 4 years, there is a persistent impact of nusinersen on clinical progression that is better observed in younger patients with higher HFMSE scores at baseline, especially during the first two years of treatment.

#1137 A Retrospective Clinical Audit of the Traffic Light Scoring System for Palliative Care in Patients with Myotonic Dystrophy Type 1

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Introduction: DM1 is a progressive multisystem disorder, leading to significant disability and premature death[1]. It is the most common muscular dystrophy in adults, with an average life expectancy of 53 years, usually from cardiorespiratory causes[2]. Multidisciplinary care is essential, yet palliative care discussions and planning are often delayed[3]. National guidelines and a recently developed traffic light system (TLS) to triage DM1 patients by disease severity, aim to address this[4].

Objectives: (1) Assess the provision and quality of palliative care for patients with myotonic dystrophy type 1 (DM1) in a specialist neuromuscular service, compared to national guidelines. (2) Identify opportunities to improve clinical monitoring and advance care planning.

Methods: A retrospective audit of 35 randomly selected DM1 patients from Salford and Withington clinics was conducted using electronic records. NIV clinic records were excluded. Clinical status was categorised via TLS. Data on diagnosis age, family history, myotonia, referrals, activities of daily living (ADLs) and advance care documentation were collected.

Results: No evidence of palliative care discussions or advance care plans was found. Most patients had a green TLS (63%), followed by amber (29%) and blue (8%). ADLs, swallowing, and bladder/bowel function were routinely assessed (>97%), but mental health was less frequently addressed (26%).

Conclusions: Prognostic discussions and planning are lacking in DM1 care. Modifying clinic templates and using additional screening tools may support earlier, integrated palliative care.

#1135 Italian validation and follow-up study of the SMA independence scale–upper limb module

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Introduction: Spinal muscular atrophy (SMA) is a progressive disorder caused by SMN1 mutations. While therapies have changed its course, current motor scales often miss aspects.

Objectives: This study aimed to validate the Italian SMA Independence Scale (SMAIS-ULM) for reliability, applicability and expansion across diverse SMA phenotypes and to explore 12 months changes in correlation to different outcome measures.

Methods: Patients with genetically confirmed 5qSMA were recruited from 12 Italian centers. Analyses included intraclass Correlation Coefficients (ICCs) for test-retest reliability, Kruskal-Wallis for group comparisons, and Spearman correlations with functional measures. Ceiling/floor effects were defined as ≥85% of a group reaching the maximum or minimum score.

Results: The study analyzed 472 completed questionnaires: 263 from caregivers (29 SMA I, 123 SMA II, 104 SMA III, 7 presymptomatic) and 209 from patients (3 SMA I, 101 SMA II, 104 SMA III; 1 SMA IV), including 195 matched caregiver-patient pairs. ICC was conducted in 29 caregivers and 31 patients, values ranged from 0.97 to 1.00. SMAIS-ULM scores differed by SMA type, with SMA III/presymptomatic subjects scoring higher than SMA I/II ($p < 0.001$) and walkers scoring higher than sitters/non-sitters ($p < 0.001$). Floor effects were found in 18.9% of non-sitters and 50% of walkers. Strong correlations with functional measures were found, with no significant differences between caregiver and patient reports.

Conclusions: The findings confirm the reliability and validity of the SMAIS-ULM as an effective tool for measuring functional independence in individuals with SMA, both from the caregiver and patient perspectives.

#1134 From Nerve to Brain: Toward a Mechanistic Understanding of Spinal Cord Stimulation in Human Subjects

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Introduction: Spinal cord stimulators (SCS) are commonly used to treat refractory neuropathic pain, although mechanisms underlying pain reduction remain unclear. Improved understanding of SCS and the development of biomarkers are critical for improving device design and optimizing patient selection.

Objectives: our hypothesis is that SCS devices reduce pain by modulating the excitability of peripheral sensory nerve fibers that project within the spinal dorsal columns, and this effect can be leveraged for biomarker development.

Methods: this is a multicenter prospective study in two patient cohorts, namely patients who currently have stably implanted spinal cord simulators (Aim 1) and patients who are planning to undergo spinal cord implantation (Aim 2). We will apply specialized tests of peripheral nerve excitability, threshold tracking nerve conduction studies (TTNS), to detect changes in the excitability exerted on these neurons by SCS. We will also perform secondary measurements to determine other potential mechanisms of SCS in the peripheral and central nervous systems.

Results: the objective of Aim 1 is to establish the relationship between pain metric changes, effected by toggling SCS stimulation, and excitability measurements by TTNS. The objective of Aim 2 is to determine whether changes in peripheral nerve excitability are predictors for response to SCS. TTNS will be performed at baseline and at 3- and 6-months post-implantation

Conclusions: successful completion of this study will yield new mechanisms by which SCS reduces pain, relevant biomarkers, and further development of promising outcomes for broad pain research.

#1133 Exercise in Facioscapulohumeral muscular dystrophy (FSHD): a UK survey of patient practice and clinical guidance

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Introduction: Facioscapulohumeral muscular dystrophy (FSHD) leads to progressive muscle weakness, pain, fatigue, and deconditioning. Exercise is increasingly recognised as beneficial, yet clinical guidelines remain limited.

Objectives: To explore UK exercise practices and clinical recommendations to inform national guidance.

Methods: An online survey (Feb–Apr 2023) was conducted as part of a broader study on FSHD conservative non-pharmacological management, open to UK FSHD adults and adult services. This analysis focused on exercise-related responses.

Results: 138 people with FSHD (PwFSHD) and 12 services responded. Among PwFSHD, 41.3% reported exercising, mainly stretching (78.8%), followed by strength (46.2%), core (38.9%), and aerobic training (28.8%). Services most frequently recommended general physical activity (100%), stretching (90.9%), and aerobic training (72.7%). Stretching was typically advised daily for ≤10 minutes (54.5%), though PwFSHD reported varied routines. Strength training was recommended 3x/week (45.5%), for 10-20 minutes; PwFSHD mostly trained 2x/week (27.9%) for <10 minutes (28.6%). Intensity was largely self-guided. Aerobic exercise was recommended 3x/week (40.0%) and performed 2x/week (44.8%) for 20-30 minutes. Intensity was rarely measured: PwFSHD used time (50.0%) or didn't measure (42.9%); services used perceived exertion (72.7%), or didn't measure (27.3%).

Conclusions: Nearly 60% of PwFSHD were not exercising. Active lifestyles and daily stretching were most recommended. Strength training was less frequently prescribed but widely performed. Both aerobic and strength training were under-prescribed and poorly monitored. Inconsistencies between – and variability within – current practices and recommendations, likely influenced by limited access, monitoring, and guidance, highlight the need for clear recommendations to support safe, effective, and appropriately dosed exercise.

#1128 Clinical Utility of Serum Neurofilament Light Chain in Peripheral Neuropathy

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Introduction: Blood-based neurofilament light chain (NfL) has emerged as a potential biomarker of neuronal injury in peripheral neuropathy (PN). Most prior studies have utilized the Quanterix Simoa® assay. However, the clinical utility of serum NfL (sNfL) in PN using commercially available laboratory remains underexplored.

Objectives: To evaluate the clinical utility of sNfL for diagnosing PN, monitoring disease activity, and assessing treatment response using a commercially available assay (Roche Diagnostics Electrochemiluminescence Immunoassay (ECLIA)).

Methods: Retrospective cohort study at the University of Pennsylvania from October 2024 to March 2025. Patients with, or at risk for, PN who underwent sNfL testing were included. Demographics, PN etiology, clinical findings, and sNfL levels were analyzed.

Results: 123 patients were included: 40 with chronic inflammatory demyelinating polyneuropathy (CIDP), 35 with transthyretin amyloidosis (TTR), 13 with vasculitic PN, 12 with Charcot-Marie-Tooth disease (CMT), 6 with multifocal motor neuropathy (MMN), 4 with anti-MAG neuropathy, and 12 with other PN types. Of these, 112 had definite large fiber PN; 14 were asymptomatic TTRv carriers. Elevated sNfL levels were detected in 24 patients (21%). Among CIDP patients, elevated sNfL was frequently seen in untreated or treatment-refractory cases and declined in response to therapy. sNfL also appeared helpful in monitoring active vasculitic PN and showed reductions following treatment initiation in patients with hATTR PN. In contrast, sNfL added limited value in most other PN etiologies.

Conclusions: Routine sNfL testing is not warranted in most PN patients. However, in select cases—such as treatment-naïve and refractory CIDP, active vasculitic PN, and hATTR—sNfL may provide useful adjunctive information to guide therapeutic decision-making.

#1123 Engineered Liposomal Formulation of GM1 Ganglioside as a Promising Treatment for ALS

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Introduction: Efficiently delivering therapeutic molecules to the brain remains a critical challenge, particularly for neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS). The blood-brain barrier (BBB) significantly limits drug penetration, preventing many promising compounds from reaching neuronal targets. Characterized by rapid motoneuron degeneration, ALS is known to involve complex pathophysiological mechanisms including mitochondrial dysfunction, endoplasmic reticulum (ER) stress, oxidative stress and neuroinflammation. As current treatments are largely ineffective, novel therapeutic strategies are urgently required.

Objectives: Nanotechnology-based drug delivery offers a promising approach to overcoming the BBB and enhancing therapeutic efficacy. GM1 ganglioside, a glycosphingolipid with neuroprotective properties, has shown therapeutic potential in Parkinson's and Huntington's disease models. However, its clinical application has been hindered by poor pharmacokinetics and limited BBB permeability. To address these limitations, we took advantage of a new liposomal formulation of GM1 named Talineuren (TLN), which promised efficient brain penetration.

Methods: Using patient-derived induced motoneurons and ALS mouse models (C9-500 and SOD1-G93A) we assessed TLN neuroprotective effects in motor behavior and observed improvement of neuropathological hallmarks at histopathological levels.

Results: Proteomic analyses revealed that TLN modulated mitochondrial and ER-related pathways, reduced ER stress, and enhanced synaptic protein expression. In vivo validation confirmed its therapeutic potential, demonstrating neuroprotection in ALS models. Furthermore, comparative proteomics between human and murine ALS models identified conserved disease-specific changes targeted by TLN.

Conclusions: The promising findings of this study, and their translational nature, support TLN as an effective candidate for ALS treatment.

#1082 Motor Unit Magnetic Resonance Imaging (MUMRI) as a novel biomarker in Spinal Muscular Atrophy (SMA)

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Introduction: Motor unit MRI (MUMRI) is a novel technique, which non-invasively detects fasciculation, a common symptom of spinal muscular atrophy (SMA).

Objectives: We aimed to evaluate feasibility of MUMRI in SMA.

Methods: 10 patients (all SMA III;6 male), 10 age comparable and sex matched controls. Images of the tongue, upper right arm, paraspinal and bilateral lower limbs were acquired using 3-point Dixon and MUMRI (pulsed gradient spin echo) sequences. Fat fraction and fasciculation rates were calculated using in-house algorithms.

Results: At group level, fat fraction was higher in SMA vs controls: arm (35.0 ± 25.4 vs 4.2 ± 1.1, $p<0.0001$), paraspinal (41.4 ± 31.0 vs 7.4 ± 4.5, $p=0.002$), thighs (54.8 ± 23.8 vs 5.7 ± 1.0, $p<0.0001$), calves (29.6 ± 23.5 vs 4.4 ± 0.9, $p=0.0003$) and tongue (13.9 ± 3.2 vs 13.0 ± 3.3, $p=0.393$). Fasciculation rate (number of signal voids per cm^3 muscle tissue per minute, $cm^{-3}min^{-1}$) was higher in SMA vs controls: arm (0.28 ± 0.61 vs 0.002 ± 0.001, $p=0.014$), paraspinal (0.06 ± 0.06 vs 0.003 ± 0.005, $p=0.001$), thighs (0.46 ± 0.57 vs 0.008 ± 0.005, $p=0.002$), calves (0.37 ± 0.58 vs 0.02 ± 0.02, $p=0.001$) and tongue (0.17 ± 0.17 vs 0.05 ± 0.08, $p=0.082$).

Conclusions: Paraspinal fat fraction was significantly higher in patients, a novel finding in SMA III. Significantly higher fasciculation rates were detected in cervical, thoracic and lumbar innervated muscles, but not bulbar. MUMRI has potential as a non-invasive biomarker to monitor progression & response in clinical trials of SMA.

#1354 Discovery and treatment of action potential-independent myotonia in hyperkalemic periodic paralysis

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Introduction/Objectives: Hyperkalemic periodic paralysis (hyperKPP) is characterized by attacks of transient weakness. A subset of hyperKPP patients suffer from transient involuntary contraction of muscle (myotonia). The goal of this study was to determine mechanisms causing myotonia in hyperKPP.

Methods: Intracellular electrophysiology, single-fiber Ca2+ imaging and whole muscle contractility studies were performed in a mouse model of hyperKPP.

Results: Myotonia in hyperkPP was caused by both involuntary myogenic action potentials (AP myotonia) lasting less than 5 minutes and action potential-independent myotonia (non-AP myotonia) lasting over one hour. Non-AP myotonia was caused by prolonged subthreshold depolarization and elevated intracellular Ca2+ in the absence of action potentials. Treatment with dantrolene effectively mitigated non-AP myotonia, suggesting that the source of Ca2+ was the sarcoplasmic reticulum. Although non-AP myotonia occurred in the absence of action potentials, Na+ channel blockers were effective as therapy.

Conclusions: We propose myotonia in hyperKPP occurs via two mechanisms: 1) suprathreshold depolarization triggering action potentials that are detectable with EMG, and 2) sustained subthreshold depolarization resulting in Na+ overload and Ca2+ leak from the sarcoplasmic reticulum. Notably, clinical diagnostics such as EMG cannot detect the second mechanism as it occurs in the absence of action potentials. Currently only a minority of patients with hyperKPP are treated with Na+ channel blockers and none are treated with dantrolene. Our data suggest hyperKPP patients, as well as patients with a number of other neuromuscular disorders, may benefit from trials of these therapies, even if they do not have myotonia detectable clinically or by EMG.

IV. Industry-Sponsored

Clinical Trials and Studies

#1291 Outcomes for Patients With Generalized Myasthenia Gravis (gMG) Prescribed Ravulizumab or Efgartigimod Treatment: A Retrospective Medical Record Analysis

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Introduction: Ravulizumab (terminal complement inhibitor) and efgartigimod (neonatal Fc receptor blocker) are approved to treat anti-acetylcholine receptor antibody-positive (AChR-Ab+) gMG. However, there is a lack of real-world data assessing clinical outcomes among patients treated with these therapies.

Objectives: Evaluate outcomes among patients with gMG treated with ravulizumab or efgartigimod as first targeted immunotherapy.

Methods: Physician-abstracted electronic medical records were included for adults with AChR-Ab+ gMG in Cardinal Health's Neurology Provider Extended Network who initiated their first targeted immunotherapy on or after December 1, 2021. Outcomes included clinical characteristics, concomitant medication use, and Myasthenia Gravis Activities of Daily Living (MG-ADL) total scores up to 2 years preinitiation and after treatment initiation.

Results: Data were available for 152 patients (ravulizumab, n=45; efgartigimod, n=107). Mean±SD age at initiation was 61.5±13.6 years for the ravulizumab group and 57.0±16.6 for the efgartigimod group. Preinitiation, mean±SD MG-ADL total scores were 9.3±2.9 in the ravulizumab group and 8.7±3.8 in the efgartigimod group. Mean±SD MG-ADL total scores at 3- and 6-months post initiation were 4.7±3.1 and 2.0±1.8 with ravulizumab and 5.6±3.4 and 4.3±3.2 with efgartigimod, respectively. Among patients taking oral corticosteroids (OCS) at treatment initiation, 17/19 (89.5%) ravulizumab patients and 33/46 (71.7%) efgartigimod patients reduced their dose during treatment. No patients increased their OCS dose while on ravulizumab, and 3/46 (6.5%) efgartigimod patients increased OCS dose to >20 mg/day.

Conclusions: Despite varying patient characteristics, results suggest both treatments improved patient outcomes and decreased OCS dosing. Patients who received ravulizumab trended toward greater improvements in MG-ADL total score than those who received efgartigimod.

Author Disclosures: CAS has consulted for Alexion and CSL Behring. SPM has served as a consultant for AbbVie, Alexion, argenx, Catalyst, Grifols, KabaFusion, Supernus, and UCB. NS is a paid speaker for Alexion and Catalyst. KSY is an employee of Alexion, AstraZeneca Rare Disease, and holds stock or stock options in AstraZeneca and Takeda. CS is an employee of Alexion, AstraZeneca Rare Disease, and holds stock or stock options in AstraZeneca. MB is an employee of Alexion, AstraZeneca Rare Disease, and holds stock or stock options in AstraZeneca. NN is an employee of Alexion, AstraZeneca Rare Disease, and holds stock or stock options in AstraZeneca. DG is an employee of Cardinal Health, which received funding to conduct this research. JS is an employee of Cardinal Health, which received funding to conduct this research. PP is an employee of Cardinal Health, which received funding to conduct this research. MTP has received compensation for medical advisory board membership or regional advisory board participation from Alexion, AstraZeneca Rare Disease, argenx, Catalyst, CSL Behring, Immunovant, and UCB.

Funding Statement: Alexion, AstraZeneca Rare Disease, funded this study.

#1290 INCIDENCE AND OUTCOME OF MENINGOCOCCAL INFECTION WITH ECULIZUMAB OR RAVULIZUMAB IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS OR NEUROMYELITIS OPTICA SPECTRUM DISORDER: AN UPDATED ANALYSIS OF US CLINICAL PRACTICE

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Introduction: Eculizumab and ravulizumab are approved therapies for generalized myasthenia gravis (gMG) and neuromyelitis optica spectrum disorder (NMOSD). Vaccinations and antibiotic prophylaxis are used to reduce the risk of Neisseria meningitidis (Nm) infection associated with these treatments.

Objectives: Provide an update to US exposure-adjusted Nm infection and mortality rates in eculizumab- or ravulizumab-treated patients with gMG and NMOSD using post-marketing pharmacovigilance data (Nm case counts) and commercial data (exposure).

Methods: The Alexion safety database was searched for eculizumab and ravulizumab (data cutoff: October and December 2024, respectively) across approved indications (gMG, NMOSD, paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome) using the MedDRA high-level term “Neisseria infection.” Only Nm-associated cases in the US were included. Reporting rates were calculated cumulatively per 100 patient-years (PY).

Results: By 2024, cumulative US eculizumab and ravulizumab exposures (PY) were 36,544 and 15,710, respectively. Cumulative US Nm infection and mortality rates remained stable over time across approved indications in both eculizumab and ravulizumab-treated patients (eculizumab: 0.13 and 0.01, respectively; ravulizumab: 0.06 and 0.01, respectively). US post-marketing Nm infection rates in eculizumab-treated patients with gMG and NMOSD were 0.04 (exposure: 10,214 PY) and 0.08 (exposure: 2,568 PY), respectively. At data cutoff, in US patients with gMG or NMOSD, there were 0 Nm infections among ravulizumab-treated patients and 0 Nm fatalities among eculizumab- or ravulizumab-treated patients.

Conclusions: Nm infection and mortality reporting rates for US eculizumab- and ravulizumab-treated patients remained stable despite increasing treatment exposure over time. These results suggest US Nm-related risk mitigation strategies are effective in patients receiving eculizumab or ravulizumab.

Disclosures: SP, LJ, FY, KG, MK, SQ and CCI are employees of Alexion, AstraZeneca Rare Disease, and hold stock or stock options in AstraZeneca.

Acknowledgements: This analysis is an update of previously presented data (Pandya et al. AANEM, 2024). This study is sponsored by Alexion, AstraZeneca Rare Disease.

#1289 Assessing Efficacy and Safety of Gefurulimab in Generalised Myasthenia Gravis: Baseline Characteristics From PREVAIL

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Introduction: Complement component 5 (C5) inhibitors are effective treatments for anti-acetylcholine receptor antibody-positive (AChR-Ab+) generalised myasthenia gravis (gMG). Gefurulimab (ALXN1720) is a new investigational C5 inhibitor designed for weekly subcutaneous (SC) self-injection.

Objectives: The ongoing phase 3, multicentre, randomised, double-blind, placebo-controlled PREVAIL study is evaluating the efficacy and safety of gefurulimab in adults with AChR-Ab+ gMG (NCT, NCT05556096; EudraCT, 2023-508284-77-00). Here, we describe summary baseline characteristics of participants in the PREVAIL study.

Methods: Adult patients with AChR-Ab+ gMG were randomised 1:1 to weekly SC self-injection of gefurulimab or placebo. The study consists of an initial screening period (up to 4 weeks), a randomised controlled treatment period (26 weeks), and an open-label extension (up to 105 weeks). Patients may continue previously prescribed allowed therapies, including immunoglobulins. The primary endpoint is change from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) total score at week 26. Secondary endpoints include change from baseline in Quantitative Myasthenia Gravis (QMG) total score and Myasthenia Gravis Composite (MGC) total score. Safety, pharmacokinetics, pharmacodynamics, immunogenicity, and quality of life are also assessed.

Results: As of 09Dec2024, 260 participants have been enrolled. At baseline (n=259), ~60% of participants were female and mean±SD MG-ADL total score was 9.0±2.2. At first dose of study intervention (n=259), mean±SD age was 52.8±15.8 yrs, and ~83% of patients were using any immunosuppressive therapy.

Conclusions: This study examines the potential of gefurulimab as an effective treatment for patients with AChR-Ab+ gMG self-administered once-weekly as a SC injection. Additional baseline characteristics will be presented.

Author Disclosures: FS:speaking honoraria/ad board/consulting fees/PI-clinical trials:Alexion, Amgen, argenx, AstraZeneca, Alexis, Biogen, Dianthus, Genpharm, Immunovant, JnJ, Leadiant, Lexeo, MedPharm, Medison, Neopharm Israel, Novartis, Prilena, Reata, RemeGen, Roche, Sandoz, Sanofi, Takeda, UCB, Zai Lab. KG:honoraria: AcademicCME, Alexion, AstraZeneca Rare Disease, Amgen, argenx, UCB. MM:honoraria/ad boards:Alexion Pharma GK, AstraZeneca Rare Disease, argenx, Asahi Kasei Medical, Hanall Biopharma, Japan Blood Products Organization, Takeda, UCB. AAH:research support: Alexion, AstraZeneca Rare Disease, argenx, Cabaletta, Genentech/Roche, Immunovant, Pfizer, Regeneron, UCB, Viela. SP:honoraria/research/travel grants/consulting fees:Adoc, Amgen, argenx, AstraZeneca, Berlin Chemie, Biogen Idec, Dianthus, Genesis, Immunabs, Kedrion, Medis, Ministry of Science of the Republic of Serbia, Mylan, Octapharma, Pfizer, Roche, Salveo, Sanofi, Swixx, Takeda, Teva Actavis, Vemax, Worwag. SR,JS,SS:Alexion, AstraZeneca Rare Disease employees; stock/stock options:AstraZeneca. JFH:research support/honoraria/consulting&nonfinancial fees:AcademicCME, Ad Scientiam, Alexion, AstraZeneca Rare Disease, Amgen, argenx, Biohaven, Biologix, Cartesian Therapeutics, CDC, CheckRare CME, CoreEvitas, Curie.bio, Medscape CME, EMD Serono, MGFA, Muscular Dystrophy Association, NIH, NMD Pharma, Novartis, PCORI, PeerView/ Physicians' Education Resource/PlatformQ CME, Regeneron, Sanofi, TG Therapeutics, Toleranzia AB, UCB, Zai Lab.

Funding Statement: Alexion, AstraZeneca Rare Disease funded this study.

Acknowledgement: This data was originally presented at European Association of Neurology (EAN) 2025 Annual Meeting, June 21st-24th in Helsinki, Finland.

#1278 LONG-TERM SAFETY AND EFFICACY OF SUBCUTANEOUS EFGARTIGIMOD PH20 IN ADULT PARTICIPANTS WITH GENERALIZED MYASTHENIA GRAVIS: RESULTS OF THE ADAPT-SC+ STUDY

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Introduction: Efgartigimod, a human immunoglobulin G1 (IgG1) antibody Fc-fragment, reduces IgG levels (including pathogenic autoantibodies) through neonatal Fc receptor blockade. In the ADAPT-SC study, subcutaneous (SC) efgartigimod PH20 (coformulated with recombinant human hyaluronidase PH20) demonstrated noninferior total IgG reduction compared with efgartigimod IV in participants with generalized myasthenia gravis (gMG). Participants completing ADAPT-SC or enrolled in ADAPT+ (efgartigimod IV open-label extension [OLE]) were eligible for the ADAPT-SC+ OLE.

Objectives: Evaluate long-term safety and efficacy of efgartigimod PH20 SC in participants with gMG in ADAPT-SC+.

Methods: Efgartigimod PH20 SC 1000 mg was administered in cycles of 4 once-weekly injections. Subsequent cycles were initiated based on clinical evaluation. Myasthenia Gravis Activities of Daily Living (MG-ADL) score assessed clinical efficacy.

Results: As of December 2022, 179 participants received ≥1 efgartigimod PH20 SC dose (mean [SD] study duration, 413 [105] days). Adverse events were predominantly mild/moderate. Injection-site reactions were mild/moderate, did not lead to treatment discontinuation, and decreased in incidence with subsequent cycles. MG-ADL total score improvement from cycle baseline was observed in Week 4 of cycle 1 (mean [SE], -4.1 [0.27]) in anti-acetylcholine receptor antibody–positive participants, with consistent/repeatable improvements through cycle 9. Similar results were seen in quality-of-life measures. Approximately half (54.6%) of participants achieved minimal symptom expression (MG-ADL score, 0-1) at any time through 9 cycles. Clinical improvements were similar to those seen with efgartigimod IV during ADAPT/ADAPT+. Updated analysis results will be presented at the congress.

Conclusions: Treatment with multiple cycles of efgartigimod PH20 SC was well tolerated and efficacious.

Disclosures: YH has no disclosures to report. TV has served as a speaker for Alexion, argenx, and CSL Behring; performed consulting work for argenx, Alexion/AstraZeneca, Amgen, Dianthus, Johnson & Johnson, ImmunAbs, and UCB; and participated in trials in MG sponsored by Alexion/AstraZeneca, argenx, UCB, Amgen, COUR, Immunovant, Regeneron, Johnson & Johnson, Dianthus, NMD Pharma, and Cartesian Therapeutics. RB-S has

served on advisory boards for argenx and is a consultant to Amgen. JLDB has served as a consultant for argenx, Alexion Pharmaceuticals, Inc., CSL, UCB Pharma, Alnylam Pharmaceuticals, Inc., Janssen, and Sanofi Genzyme. CA has received funding for travel, meeting attendance, and advisory board participation from Alexion, Momenta, Sanofi, Janssen, argenx, and UCB. AM has received speaker honoraria from Alexion Pharmaceuticals, Inc, argenx, Grifols, SA, and Hormosan Pharma GmbH; honoraria from argenx, Alexion Pharmaceuticals, Inc, UCB, Janssen, and Merck for consulting services; and financial research support (paid to his institution) from Octapharma, argenx, and Alexion Pharmaceuticals, Inc. He is a member of the medical advisory board of the German Myasthenia Gravis Society. KU has served as a paid Consultant for UCB Pharma, Janssen Pharma, Horizon Therapeutics (Viela Bio), Chugai Pharma, Hanall BioPharma, Merck, and Mitsubishi Tanabe Pharma, and has received speaker honoraria from argenx BV, Alexion Pharmaceuticals, UCB Pharma, and the Japan Blood Products Organization. W-YH, RHJ, FMV, MJ, and MH are employees of argenx. DK has received speaker honoraria from Roche, Novartis Russia, Sanofi, Merck, Janssen (Johnson & Johnson company); research grants from Novartis, UCB, argenx BV, Viela Bio Inc. (now Horizon Therapeutics), and Bristol-Mayers-Squib; and was compensated for consulting and serving on scientific advisory boards for Novartis Russia, Janssen (Johnson & Johnson company), and BIOCAD. AK-P has received honoraria for lectures and travel support, consulting fees from CSL Behring, Kedrion, Takeda, argenx, Medison, AstraZeneca, UCB, Roche, Biogen, Novartis; research support from Takeda, Sanofi and Biogen. JJGMV receives financial support from Target to B consortium, Prinses Beatrix Spierfonds, and has been involved in trials or consultancies for argenx, Alexion, NMD Pharma. The LUMC received royalties from IBL and funding from argenx for MG research. All reimbursements were received by the LUMC. He is co-inventor on patent applications based on MuSK-related research. The author is a member of the European Reference Network for Rare Neuromuscular Diseases [ERN EURO-NMD]. HW receives honoraria from AbbVie, Alexion, argenx, Bristol Myers Squibb/Celgene, Janssen, Merck, and Novartis and received speaker honoraria and travel support from Alexion, Biogen, Bristol Myers Squibb, F. Hoffmann-La Roche Ltd., Genzyme, Merck, Neurodiem, Novartis, Roche Pharma AG, TEVA, and WebMD Global. He is a paid consultant for AbbVie, Actelion, argenx, Biogen, Bristol Myers Squibb, EMD Serono, Fondazione Cariplo, Gossamer Bio, Idorsia, Immunic, Immunovant, Janssen, Lundbeck, Merck, NexGen, Novartis, PSI CRO, Roche, Sanofi, Swiss Multiple Sclerosis Society, UCB, and Worldwide Clinical Trials. He receives research funding from German Ministry for Education and Research (BMBF), Deutsche Forschungsgesellschaft (DFG), Deutsche Myasthenie Gesellschaft e.V., Alexion, Amicus Therapeutics Inc., argenx, Biogen, CSL Behring, F. Hoffmann - La Roche, Genzyme, Merck KgaA, Novartis Pharma, Roche Pharma, and UCB Biopharma. JFH has received research funding (paid to his institution) from Ad Scientiam, Alexion AstraZeneca Rare Disease, argenx, Cartesian Therapeutics, Centers for Disease Control and Prevention, MGFA, Muscular Dystrophy Association, NIH, NMD Pharma, and UCB Pharma; honoraria/consulting fees from AcademicCME, Alexion AstraZeneca Rare Disease, Amgen, argenx, Biohaven Ltd, Biologix Pharma, CheckRare CME, CoreEvitas, Curie.bio, Hansa Biopharma, Medscape CME, Merck EMB Serono, Novartis Pharma, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron Pharmaceuticals, Sanofi US, Seismic Therapeutics, TG Therapeutics, Toleranzia AB, and UCB Pharma; non-financial support from Alexion AstraZeneca Rare Disease, argenx, Biohaven Ltd, Cartesian Therapeutics, Toleranzia AB, and UCB Pharma.

#1258 Phase 3 Myasthenia Gravis Inebilizumab Trial (MINT): Efficacy Data in AChR+ Generalized MG Subpopulation through Week-52

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Introduction: The MINT primary efficacy endpoint, the change in Myasthenia Gravis Activities of Daily Living (MG-ADL) score at Week-26 in the combined population of acetylcholine receptor antibody-positive (AChR+) and muscle-specific kinase antibody-positive (MuSK+) was achieved supporting the efficacy of inebilizumab in generalized myasthenia gravis (gMG).

Objectives: To investigate the efficacy and durability of inebilizumab, a monoclonal antibody targeting CD19+ B-cells, in AChR+ gMG.

Methods: MINT (NCT04524273), a phase 3 clinical trial in adults with gMG, included a protocol-required steroid taper. The randomized control period (RCP) continued through Week-52 for the AChR+ cohort and included additional secondary endpoints: change from baseline in MG-ADL and Quantitative Myasthenia Gravis (QMG) scores at Week-52 and proportion of participants that achieved ≥3-point improvement at Week-52, without use of rescue therapy between Day-28 and Week-52. AChR+ participants received 300mg of intravenous inebilizumab or placebo on RCP Day-1, Day-15, and Day-183.

Results: Out of 238 randomized participants, 190 were AChR+ (inebilizumab: 95, placebo: 95). Change from baseline in the MG-ADL score demonstrated greater improvement with inebilizumab vs. placebo at Week-52 (adjusted difference, −2.8; 95% CI, −3.9 to −1.7; nominal $p<0.001$), with 72.3% vs. 45.2% proportion of AChR+ participants improving by ≥3 points. Similarly, change from baseline in QMG score was greater in the inebilizumab group as compared to placebo at Week-52 (adjusted difference, −4.3; 95% CI, −5.9 to −2.8; nominal $p<0.001$), with 69.2% vs. 41.8% proportion of AChR+ participants improving by ≥3 points.

Conclusions: Prespecified analysis of MINT supports continued improvement and efficacy of inebilizumab in the AChR+ gMG subpopulation through Week-52.

Disclosures: R.J. Nowak receives research support from the National Institutes of Health, Genentech, Inc., Alexion Pharmaceuticals, Inc., argenx, Annexon Biosciences, Inc., Ra Pharmaceuticals, Inc. (now UCB S.A.), the Myasthenia Gravis Foundation of America, Inc., Momenta Pharmaceuticals, Inc. (now Janssen), Immunovant, Inc., Grifols, S.A., and Viela Bio, Inc. (Horizon Therapeutics, now Amgen Inc.). Served as a consultant and advisor for Alexion Pharmaceuticals, Inc., argenx, Cabaletta Bio, Inc., Cour Pharmaceuticals, Ra Pharmaceuticals, Inc. (now UCB S.A.), Immunovant, Inc., Momenta Pharmaceuticals, Inc. (now Janssen), and Viela Bio, Inc. (Horizon Therapeutics, now Amgen Inc.). K. Utsugisawa served as a paid consultant for UCB Pharma, argenx, Janssen Pharma, Viela Bio (Horizon Therapeutics, now Amgen Inc.), Chugai Pharma, Hanall BioPharma, Merck and Mitsubishi Tanabe Pharma, and has received speaker honoraria from Argenx, Alexion Pharmaceuticals, UCB Pharma and the Japan Blood Products Organization. M. Benatar receives research support from Immunovant & Alexion. Served as a consultant to Alexion, Cartesian, Canopy, CorEvitas, Horizon Therapeutics (now Amgen Inc.), Immunovant, Sanoi, Takeda, and UCB. E. Ciafaloni received compensation for serving on advisory boards and/or as a consultant for Alexion, argenx, Biogen, Amicus, Pfizer, Italfarmaco, Sarepta, Janssen, NS Pharma, and Roche. M.I. Leite funded by the NHS (Myasthenia

and Related Disorders Service and National Specialised Commissioning Group for Neuromyelitis Optica, UK) and by the University of Oxford, UK. She has been awarded research grants from the UK association for patients with myasthenia (Myaware), Muscular Dystrophy UK and the University of Oxford. She has received speaker honoraria or travel grants from Biogen, Novartis, UCB Pharma, and the Guthy-Jackson Charitable Foundation. She serves on scientific or educational advisory boards for UCB Pharma, argenx, and Horizon Therapeutics (now Amgen Inc.). J. Vissing advisor on advisory boards for Regeneron, UCB Pharma, argenx, Alexion Pharmaceuticals, Horizon Therapeutics (now Amgen Inc.), Dianthus Therapeutics, Janssen, and Roche. C. Najem, S. Cheng, Y. Wu, and F. Tang are employees of and stockholders in Amgen Inc. N. Rampal was an employee of and stockholder in Amgen Inc. at the time of the study. J.F. Howard Jr. receives research funding (paid to his institution) from Ad Scientiam, Alexion AstraZeneca Rare Disease, argenx, Cartesian, Centers for Disease Control and Prevention, MGFA, Muscular Dystrophy Association, NMD Pharma, NIH, PCORI, and UCB Pharma; honoraria/consulting fees from AcademicCME, Alexion AstraZeneca Rare Disease, Amgen, argenx, Biohaven Ltd, Biologix Pharma, CheckRare CME, CorEvitas, Curie.bio, ,–Hansa Biopharma, Medscape CME, Merck EMB Serono, Novartis Pharma, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron Pharmaceuticals, Sanofi US, TG Therapeutics and UCB Pharma; non-financial support from Alexion, argenx, Biohaven Ltd, Cartesian Therapeutics, Toleranzia AB, and UCB Pharma.

#1241 INSPIRE CMT-SORD Clinical Trial: CMT-Health Index Results at Month 18 and 24

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Introduction: Biallelic loss of function in Sorbitol dehydrogenase (SORD) results in a hereditary motor-dominant neuropathy grouped in the broader category of Charcot-Marie-Tooth Type 2 (CMT2). CMT-SORD affects approximately 3,000 patients in the United States (US). Severe sorbitol dehydrogenase deficiency leads to accumulation of sorbitol in blood and tissues. Inhibition of Aldose Reductase (AR) has been shown to lower sorbitol levels via a family of drugs called Aldose Reductase Inhibitors (ARI). Govorestat, a CNS-penetrant ARI, is being evaluated in patients with CMT-SORD. Here we show results of treating patients with CMT-SORD using the Charcot-Marie-Tooth Health Index Scale (CMT-HI) and it's components.

Objectives: To evaluate the safety and efficacy of govorestat in patients with CMT-SORD using the CMT-HI scale.

Methods: The INSPIRE study, a randomized, double-blind, placebo-controlled, multicenter, investigational trial was designed to assess the safety and efficacy of long term administration of govorestat in patients with CMT-SORD measured by whole blood sorbitol reduction, CMT-HI, and the correlation of change between the two.

Results: Fifty-six patients with CMT-SORD were randomized 2:1 ratio to govorestat 20mg/kg once daily or placebo. Twenty-six patients (46.6%) had the biallelic homozygous mutation c.757 delG (p.A253Qfs*27). The statistically significant improvement in the CMT-HI at Month 12 was sustained through Month 24.

Conclusions: CMT-SORD is a severe and progressive neuropathy caused by elevated levels of sorbitol. Govorestat remains generally safe and well tolerated.

#1235 MYASTHENIA GRAVIS INEBILIZUMAB TRIAL (MINT): REDUCED RISK OF MG EXACERBATIONS, RESCUE THERAPY USE, AND CORTICOSTEROID BURDEN

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Introduction: Generalized Myasthenia Gravis (gMG) is characterized by fluctuating weakness and by autoreactive B-cells playing an essential role in upstream immunopathogenesis. The MINT (NCT04524273) primary endpoint was achieved supporting the efficacy of inebilizumab in gMG. MG exacerbations, which may lead to life-threatening respiratory failure, and rescue therapy use are a significant burden on health care resources and patients.

Objectives: To determine if inebilizumab reduces the risk of disease exacerbations and rescue therapy (RT) use in patients with gMG.

Methods: The randomized controlled period (RCP) was 52-weeks for AChR+ and 26-weeks for MuSK+ populations. Participants received 300mg of inebilizumab or placebo on RCP Day-1, Day-15, and Day-183 (AChR+ only). Participants on prednisone underwent a protocol-required steroid taper to ≤5mg/day. Secondary endpoints included risk of exacerbations and use of RT at Week-26 and Week-52 (primary analysis).

Results: 119 participants were randomized to inebilizumab; 119 to placebo. At baseline, the mean steroid dose (mg/day) was comparable between treatment groups. At Week-26, mean steroid dose was reduced in both treatment groups. Inebilizumab-treated participants experienced lower risk of exacerbation than placebo through Week-26 ([Hazard Ratio, 95% CI, nominal p-value]; combined:0.41(0.24-0.70), p=0.001; AChR+:0.49(0.27-0.90), p=0.021; MuSK+:0.21(0.06, 0.79), p=0.020) and Week-52 in AChR+ (0.40[0.23-0.70], p=0.001). Fewer participants in the inebilizumab group used RT compared to placebo through Week-26 (inebilizumab vs. placebo, nominal p-value, combined:8.4% vs. 23.9%, p=0.005; AChR+:9.5% vs. 23.7%, p=0.016; MuSK+:4.2% vs. 25.0%, p=0.191) and Week-52 in AChR+ (11.6% vs. 34.4%, p=0.005).

Conclusions: Inebilizumab treatment reduced risk of MG exacerbation and RT use while successfully tapering steroid.

Disclosures: R.J. Nowak receives research support from the National Institutes of Health, Genentech, Inc., Alexion Pharmaceuticals, Inc., argenx, Annexon Biosciences, Inc., Ra Pharmaceuticals, Inc. (now UCB S.A.), the Myasthenia Gravis Foundation of America, Inc., Momenta Pharmaceuticals, Inc. (now Janssen), Immunovant, Inc., Grifols, S.A., and Viela Bio, Inc. (Horizon Therapeutics, now Amgen Inc.). Served as a consultant and advisor for Alexion Pharmaceuticals, Inc., argenx, Cabaletta Bio, Inc., Cour Pharmaceuticals, Ra Pharmaceuticals, Inc. (now UCB S.A.), Immunovant, Inc., Momenta Pharmaceuticals, Inc. (now Janssen), and Viela Bio, Inc. (Horizon Therapeutics, now Amgen Inc.). K. Utsugisawa served as a paid consultant for UCB Pharma, argenx, Janssen Pharma, Viela Bio (Horizon Therapeutics, now Amgen Inc.), Chugai Pharma, Hanall BioPharma, Merck and Mitsubishi Tanabe Pharma, and has received speaker honoraria from Argenx, Alexion Pharmaceuticals, UCB Pharma and the Japan Blood Products Organization. M. Benatar receives research support from Immunovant & Alexion. Served as a consultant to Alexion, Cartesian, Canopy, CorEvitas, Horizon Therapeutics (now Amgen Inc.), Immunovant, Sanoi, Takeda, and UCB. E. Ciafaloni received compensation for serving on advisory boards and/or as a consultant for Alexion, argenx, Biogen, Amicus, Pfizer, Italfarmaco, Sarepta, Janssen, NS Pharma, and Roche. M.I. Leite funded by the NHS (Myasthenia and Related Disorders Service and National Specialised Commissioning Group for Neuromyelitis Optica, UK) and by the University of Oxford, UK. She has been awarded research grants from the UK association for patients with

myasthenia (Myaware), Muscular Dystrophy UK and the University of Oxford. She has received speaker honoraria or travel grants from Biogen, Novartis, UCB Pharma, and the Guthy-Jackson Charitable Foundation. She serves on scientific or educational advisory boards for UCB Pharma, argenx, and Horizon Therapeutics (now Amgen Inc.). J. Vissing advisor on advisory boards for Regeneron, UCB Pharma, argenx, Alexion Pharmaceuticals, Horizon Therapeutics (now Amgen Inc.), Dianthus Therapeutics, Janssen, and Roche. F. Tang, Y. Wu, C. Najem, S. Cheng are employees of and stockholders in Amgen Inc. J.F. Howard Jr. receives research funding from Ad Scientiam, Alexion AstraZeneca Rare Disease, argenx, Cartesian, Centers for Disease Control and Prevention, MGFA, Muscular Dystrophy Association, NMD Pharma, NIH, PCORI, and UCB Pharma; honoraria/consulting fees from AcademicCME, Alexion AstraZeneca Rare Disease, Amgen, argenx, Biohaven Ltd, Biologix Pharma, CheckRare CME, CorEvitas, Curie.bio, F. Hoffmann-LaRoche Ltd, Medscape CME, Merck EMB Serono, Novartis Pharma, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron Pharmaceuticals, Sanofi US, TG Therapeutics UCB Pharma, and Zai Labs; non-financial support from Alexion, argenx, Biohaven Ltd, Cartesian Therapeutics, Toleranzia AB, UCB Pharma and Zai Labs.

#1234 Update on INSPIRE DUCHENNE: A Phase 1/2 Study of SGT-003, an Investigational Next-Generation Microdystrophin Gene Therapy for Duchenne Muscular Dystrophy

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Introduction: Duchenne is a chronic, progressive, and ultimately fatal neuromuscular disorder resulting from the lack of functional dystrophin protein. SGT-003 is a next-generation investigational AAV-based gene therapy that aims to replace dystrophin and stabilize muscle using a unique functional microdystrophin.

Objectives: INSPIRE DUCHENNE is a first-in-human phase 1/2, open-label, multicenter, clinical trial to evaluate the safety, tolerability, and efficacy of a single intravenous infusion of SGT-003 at 1E14 vg/kg in pediatric patients with Duchenne.

Methods: SGT-003 was designed to better target muscles and reduce liver uptake compared to first generation approaches by using a next-generation muscle-tropic capsid, AAV-SLB101. It delivers a unique microdystrophin that includes the nNOS binding domain, responsible for protection against ischemia-induced muscle injury. Results from the first participants enrolled in INSPIRE DUCHENNE were analyzed for safety and biomarker evaluation.

Results: As of a May 30, 2025 data cutoff, SGT-003 has been well tolerated in 12 study participants. There have been no reports of TE-SAEs, and all TR-AEs resolved without sequelae in the weeks following dosing. No biomarker or clinical evidence of liver injury was observed. High levels of transduction and microdystrophin expression were observed at Day 90 in muscle biopsies from the first 3 participants, with means of 18.7 for VCN, 110% of normal dystrophin by Western blot, and 78% of microdystrophin-positive fibers. Improvements in multiple biomarkers of muscle integrity were also observed.

Conclusions: These initial results suggest a favorable safety profile and preliminary biomarker changes following a single dose of SGT-003 in pediatric patients with Duchenne.

#1233 SGT-003: Initial Safety Evaluation of a Next-Generation Investigational Gene Therapy for Duchenne Muscular Dystrophy

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Introduction: Adeno-associated virus (AAV) vectors have emerged as a promising tool for gene therapy due to their ability to deliver genetic material with high precision. However, high systemic doses currently required to achieve widespread therapeutic benefit for neuromuscular indications can pose potential safety risks, including acute serious liver injury. To address this issue, capsids can be engineered to refine and enhance their tropism to tissues of interest, while de-targeting the liver. In particular, AAV-SLB101, a next-generation rationally designed capsid, has shown increased skeletal and cardiac muscle tropism and decreased biodistribution to the liver in preclinical studies.

Objectives: To interrogate preliminary safety and tolerability data from the INSPIRE DUCHENNE (NCT06138639) Phase 1/2 study of SGT-003, which utilizes AAV-SLB101.

Methods: A number of biomarkers, including evaluation of multiple liver enzymes, were used to longitudinally assess safety in human patients with Duchenne muscular dystrophy following administration of SGT-003.

Results: Preliminary data from the INSPIRE DUCHENNE trial suggest high levels of biodistribution and microdystrophin expression in muscle biopsies collected at Day 90 for the first 3 participants, and as of May 30, 2025, no biomarker or clinical evidence of liver injury have been observed (N=12).

Conclusions: The initial safety and tolerability profile of SGT-003 has been favorable in the 12 participants dosed as of May 30, 2025, with no treatment-emergent serious adverse events observed and all treatment-related adverse events resolved without sequelae in the weeks following dosing. We hypothesize this may be attributed to AAV-SLB101's reduced liver biodistribution seen in nonclinical studies.

#1232 AAV-SLB101 in Duchenne Muscular Dystrophy: Nonclinical Safety and Efficacy Characterization and Preliminary Clinical Insights

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Introduction: AAV-mediated gene therapy remains a promising therapeutic approach for multiple neuromuscular indications. Currently, high systemic doses are needed to achieve therapeutic benefit for conditions like Duchenne; however, high viral load can pose safety risks.

Objectives: To develop a more targeted and efficacious vector, AAV-SLB101 was rationally designed to increase muscle tropism and is presently utilized in Solid Biosciences' next generation, investigational gene therapy SGT-003, which is currently in a clinical study for the treatment of Duchenne (INSPIRE DUCHENNE; NCT06138639)

Methods: A comprehensive panel of studies across mice, non-human primates, human cell lines and clinical trial participants was compiled to explore both efficacy and safety of AAV-SLB101.

Results: AAV-SLB101 demonstrated increased muscle tropism and decreased liver uptake in healthy animals and disease models (wild type and mdx mice, non-human primates, and human iPSC-derived cardiomyocytes) compared to first-generation vectors. Early findings in the Phase 1/2 INSPIRE DUCHENNE trial showed high microdystrophin expression, with an average of 110% of normal dystrophin detected via Western blot in the first 3 participants at 90 days post-treatment. Biomarker analysis revealed improvements in muscle and cardiac markers, supporting the potential of SGT-003 as a next-generation therapy. Additionally, safety assessments indicate a favorable profile with no treatment-emergent serious adverse events reported as of May 30, 2025 (n=12).

Conclusions: Extensive nonclinical and preliminary clinical data support the use of AAV-SLB101 as an innovative next-generation capsid. These findings elucidate the intricate mechanism of AAV-SLB101 and underscore its potential as a targeted gene therapy vector for neuromuscular and cardiac indications.

#1228 ClC-1 inhibition improves NMJ structure and function in CMT2D, MuSK MG and re-innervation

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Introduction: The neuromuscular junction (NMJ) is critical for muscle contraction and is disrupted in diverse neuropathies. The skeletal muscle ClC-1 chloride channel regulates membrane excitability, but its role in NMJ repair is not fully understood.

Objectives: To determine whether pharmacological inhibition of ClC-1 enhances NMJ re-innervation, synaptic transmission, and muscle function in three rodent models: a mouse model of Charcot-Marie-Tooth disease type 2D (CMT2D), a rat model of MuSK myasthenia gravis (MuSK-MG), and a rat sciatic nerve crush injury model (crush).

Methods: Animals were randomized to receive either a selective ClC-1 inhibitor (50 mg/kg) or vehicle control (blinded). NMJ re-innervation was quantified by bungarotoxin and Synaptic vesicle 2 with Neurofilament-M for co-localization (% occupancy) in MuSK MG and CMT2D. Electrophysiological assessments were performed by compound muscle action potential (CMAP) in MuSK MG and CMT2D. Muscle performance was evaluated by grip strength (CMT2D and MuSK-MG) and gait analysis (crush).

Results: Fully innervated endplates were present in 21 % MuSK MG and 40 % CMT2D muscle when treated with vehicle, vs 46 % and 65 %, respectively, when treated with ClC-1 inhibitor. CMAP amplitude increased across all models when receiving ClC-1 inhibitor vs vehicle. Muscle grip strength improved in CMT2D and MuSK-MG cohorts, as did speed and stride regularity in crush animals.

Conclusions: ClC-1 inhibition consistently promotes NMJ re-innervation, strengthens synaptic transmission, and improves muscle function in NMJ disease- and nerve-injury models. These findings identify ClC-1 as a possible therapeutic target for enhancing NMJ repair in neuromuscular disorders to improve muscle function.

#1222 Del-zota produced statistically significant increases in exon skipping and dystrophin levels in EXPLORE44®, a Phase 1/2 study in patients with DMD44

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Introduction: Duchenne muscular dystrophy (DMD) is caused by mutations in the dystrophin gene. Delpacibart zotadirsen, or del-zota (AOC 1044), is an antibody-oligonucleotide conjugate (AOC™) comprised of an anti-transferrin receptor 1 (TfR1) antibody conjugated to an exon 44-skipping phosphorodiamidate morpholino oligomer (PMO). Del-zota is designed to restore the dystrophin reading frame and produce functional, internally truncated dystrophin protein in individuals with mutations amenable to exon 44 skipping (DMD44).

Objectives: Part B of the Phase 1/2 EXPLORE44® trial (NCT05670730) is a randomized, placebo-controlled, double-blind study assessing safety, tolerability, pharmacokinetics, and exon skipping efficacy of multiple-ascending doses of del-zota.

Methods: EXPLORE44® enrolled 24 ambulatory and non-ambulatory individuals aged 7 – 27 years with DMD44. (Part A healthy volunteer data has been reported previously).

Results: Treatment with del-zota resulted in consistent and high PMO muscle concentrations and produced significant increases in exon skipping (up to 67%) and dystrophin production (average of 25% and up to 58% of normal) in skeletal muscle and consistent reductions in blood creatine kinase to near normal levels (reduced by >80% compared to baseline). Del-zota produced favorable safety and tolerability results.

Conclusions: The EXPLORE44® trial represents the first-in-patient experience using Avidity Biosciences' proprietary AOC™ technology to deliver PMOs to muscle. Del-zota's ability to increase dystrophin production and exon skipping and reduce CK levels highlights its potential to improve the lives of patients with DMD44. These data support the continued evaluation of del-zota in the Phase 2 EXPLORE44-OLE™ trial (NCT06244082).

#1221 DMPK siRNAs Efficiently Reduce the Levels of the Nuclear-Localized Mutant CUGExp DMPK mRNA that Causes Myotonic Dystrophy Type 1

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Introduction: Myotonic dystrophy type 1 (DM1) is a rare, autosomal dominant, progressive neuromuscular disease with no approved therapies. DM1 is caused by a toxic gain-of-function CUG repeat-expansion mutation in the myotonic dystrophy protein kinase (DMPK) mRNA. At Avidity, we leveraged our Antibody Oligonucleotide Conjugate (AOC™) platform to develop an investigational product candidate for the treatment of DM1, del-desiran (delpacibart etedesiran; formerly AOC 1001). Del-desiran consists of a small interfering RNA (siRNA) targeting DMPK mRNA conjugated to a monoclonal transferrin receptor 1 (TfR1) antibody that allows for productive siRNA delivery into muscle to reduce DMPK expression.

Objectives: As the DM1-causing mutant DMPK mRNA is localized within nuclei, we sought to confirm nuclear activity of DMPK siRNAs.

Methods: We used a MALAT1-targeting siRNA as a tool to evaluate nuclear siRNA activity in human DM1 myoblasts in vitro and mouse skeletal muscle in vivo. Next, we evaluated the nuclear activity of DMPK siRNAs in cultured myoblasts derived from individuals with DM1 using subcellular fractionation and RNAscope as orthogonal methods.

Results: The MALAT1 siRNA decreased MALAT1 levels in human DM1 myoblasts and mouse skeletal muscle upon AOC treatment. DMPK siRNAs were able to reduce DMPK mRNA levels in the nuclear compartment of DM1 myoblasts and the amount of nuclear CUG^{Exp} RNA-containing foci that drive DM1.

Conclusions: DMPK siRNAs are active in the nucleus and can reduce levels of nuclear mutant DMPK mRNA, the underlying cause of DM1. These preclinical data support the ongoing evaluation of del-desiran in clinical trials for the treatment of DM1.

#1220 Topline Data from Dose Escalation Cohorts A and B in FORTITUDE™, a Phase 1/2 Trial Evaluating Del-brax (delpacibart braxlosiran) in Adults with Facioscapulohumeral Muscular Dystrophy (FSHD)

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Introduction: Delpacibart braxlosiran, or del-brax (AOC 1020) is an antibody-oligonucleotide conjugate (AOC™) composed of a DUX4-targeting siRNA conjugated to a humanized anti-transferrin receptor 1 antibody to enable targeted delivery to muscle. Del-brax is designed to target the root cause of FSHD by degrading aberrantly expressed DUX4 mRNA and reducing expression of DUX4-regulated genes.

Objectives: FORTITUDE™ (NCT05747924) is a phase 1/2 randomized, double-blind, placebo-controlled trial evaluating safety, tolerability, pharmacokinetics, and pharmacodynamics of del-brax in individuals with FSHD.

Methods: FORTITUDE™ includes three cohorts with a 1-year treatment and follow-up period. The first two cohorts (Cohort A and B; n=12 and 27, respectively) were multiple-ascending dose cohorts that evaluated 2 mg/kg (first dose 1 mg/kg) and 4 mg/kg given every 6 weeks for three doses followed by two quarterly doses. Cohort C (n=51) is a biomarker cohort evaluating 2 mg/kg given every 6-7 weeks. Cohort A and B have completed, and Cohort C is ongoing.

Results: Data will be presented for Cohorts A and B, including DUX4-regulated biomarkers, serum creatine kinase, exploratory efficacy endpoints, and long-term safety.

Conclusions: FORTITUDE™ data from Cohorts A and B support del-brax's continued clinical development as the first investigational therapy targeting the root cause of FSHD via the ongoing biomarker cohort and the initiation of a global Phase 3 study.

#1216 Comparison of Functional Outcomes of Bidridistrogene Xeboparvovec and Matched Natural History Controls in Patients With LGMD 2E/R4: Results From Phase 1 and Phase 1/2a Trials

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Introduction: Limb-girdle muscular dystrophy 2E/R4 (LGMD2E/R4) is caused by mutations in the β-sarcoglycan (SGCB) gene, leading to muscle loss. Bidridistrogene xeboparvovec, an investigational adeno-associated virus vector that delivers the full-length SGCB transgene, has shown efficacy and a manageable safety profile.

Objectives: To evaluate efficacy in studies SRP-9003-101 (NCT03652259) and SRP-9003-102 (NCT05876780) versus matched natural history (NH) controls from the JOURNEY study (NCT04475926).

Methods: Participants from SRP-9003-101 (ambulatory; n=6; cohort 1, 1.85×10^{13} vg/kg; cohort 2, 7.41×10^{13} vg/kg) and SRP-9003-102 (nonambulatory; n=5; 7.41×10^{13} vg/kg) received a single treatment infusion. JOURNEY provided an age- and function-matched external control group. This analysis evaluated the least squares means change from baseline (CFBL) difference through month 18 for North Star Assessment for LGMD (NSAD), Performance of Upper Limb (PUL) 2.0, and timed function tests as well as CFBL difference in creatine kinase (CK) at month 12 versus NH controls.

Results: In SRP-9003-101 (mean age at dosing, 10 years), a significant difference in mean CFBL was observed across multiple endpoints (NSAD and other timed function tests) versus NH controls. In SRP-9003-102 (mean age at dosing, 20.2 years), a significant difference in mean CFBL was observed in NSAD and PUL 2.0 total scores versus NH controls. Significantly reduced CK levels were observed in both studies versus NH controls. The safety profile remained consistent with prior analyses.

Conclusions: Treatment with bidridistrogene xeboparvovec showed a beneficial modification of disease trajectory compared with NH controls. Given the heterogeneity of LGMD2E, longer-term data from ongoing clinical and NH studies are needed to confirm treatment effects.

Sponsorship: Sarepta Therapeutics, Inc.

Disclosures: GC: Participated in advisory boards and as a consultant for Italfarmaco, Roche, and Sarepta Therapeutics, Inc. Served as a speaker for Sarepta Therapeutics, Inc. Served as principal investigator of studies sponsored by Atamyo, Roche, Sarepta Therapeutics, Inc., and Scholar Rock. LNA: Received fees from Sarepta Therapeutics, Inc., for licensure of the LGMD natural history data set. Participated in advisory boards for Sarepta Therapeutics, Inc. Nationwide Children's Hospital received salary support. KGC: Received speaker/advisory board honoraria from Alexion, Alnylam, Amicus Therapeutics, argenx, Biogen, CSL Behring, Ipsen, Janssen Pharmaceuticals, Lupin, Pfizer, Roche, Sanofi Genzyme, and UCB and research funding from CSL Behring and Roche. AMC: Served on an advisory board for Sarepta Therapeutics, Inc., unrelated to this work. JLDB: Received speaker/advisory board honoraria from Alexion, Alnylam, Amicus Therapeutics, argenx, Biogen, CSL Behring, Janssen Pharmaceuticals, Roche, Sanofi Genzyme, and UCB. JDM: Participated in advisory boards for Amicus, Astellas, Lupin, Sanofi, Sarepta Therapeutics, Inc., and Spark. Received funding for research from Boehringer Ingelheim, Sanofi, Sarepta Therapeutics, Inc., and Spark. RSF: Served on an advisory board and on a data safety and monitoring board for Sarepta Therapeutics, Inc., unrelated to this work. AG: Received speaker honoraria from PTC Therapeutics, Roche, and Sarepta Therapeutics, Inc. Participated in advisory boards for Italfarmaco. MKJ: Served on scientific advisory boards for Genethon, Pfizer, Roche, and Sarepta Therapeutics, Inc., and received fees for consulting and training services from Amicus, Antisense, BridgeBio, Capricor, Catabasis, Dyne, Edgewise, Italfarmaco, NS Pharma, Pfizer, PTC, Santhera, Sarepta Therapeutics, Inc., and Summit. CGL: Participated in advisory boards for Biogen, Catalyst, Dyne, Novartis, and Sarepta Therapeutics, Inc. CIOG: Participated in advisory boards for PTC Therapeutics, Sanofi, and Sarepta Therapeutics, Inc. CMP: Participated in advisory boards and as a consultant for Biogen, Genentech/Roche, Novartis Gene Therapies, Sarepta Therapeutics, Inc., and Scholar Rock. Served as a speaker for Biogen. Served as principal investigator of studies sponsored by Astellas, Biogen, Biohaven, CSL Behring, FibroGen, Novartis Gene Therapies, Pfizer, PTC, Sarepta Therapeutics, Inc., and Scholar Rock. HT: Nothing to disclose. SWY: Participated in advisory boards for Biogen and Catalyst and serves as a consultant for Passage Bio. LPL, WH, NL, LRK, JRM: Employees of Sarepta Therapeutics, Inc., and may own stock in the company.

#1215 Exploratory Biomarker Analyses in a Phase 2 Trial of Riliprubart for Chronic Inflammatory Demyelinating Polyneuropathy

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Introduction: Riliprubart, a first-in-class humanized IgG4-monoclonal antibody, selectively inhibits activated-C1s within the classical-complement pathway, and can be self-administrated subcutaneously via an auto-injector. In a phase-2 trial (NCT04658472), riliprubart treatment in participants with CIDP showed favorable benefit:risk profile and reduction in NfL.

Objectives: To report subgroup-analyses of biomarkers at W24.

Methods: This trial evaluates riliprubart in participants with CIDP: SoC-Treated/Refractory groups underwent W24 treatment (Part-A), then optional treatment extension (Part-B: W52). Part-A subgroup-analyses used baseline (BL) clinical characteristics (CIDP-subtype, time since start of therapy/diagnosis, previous therapies, Ig dose, BL NfL [tertiles for overall cohort: ≤12.40, >12.40-<29.60, ≥29.60 pg/mL) and INCAT score [≤4 or ≥4 overall median]) in SoC-Treated/Refractory groups, and all participants. At W24, geometric means (GM) ratios to BL in NfL, and INCAT response rate according to NfL absolute change from BL (categorized in tertiles), were calculated.

Results: As of April-2024, available interim-data (48 SoC-Treated/18-Refractory participants) showed overall 31% NfL reduction [GM ratio (SD), 0.69±1.67] which was similar in SoC-Refractory (0.70±1.64) and SoC-Treated (0.69±1.68) groups at W24. Similar NfL reductions observed in atypical vs. typical CIDP (0.50±1.85 vs. 0.77±1.54), high vs. low BL NfL levels (0.66±1.88 vs. 0.85±1.26), and BL INCAT scores (0.60±1.76 vs. 0.75±1.6). At W24, %-INCAT responders was higher among participants who had greater reductions from BL (SoC-Refractory: 67% [4/6]; SoC-Treated: 69% [11/16]) vs. lower reductions (SoC-Refractory: 33% [2/6]); SoC-Treated: 31% [5/16]). Available data will be presented at meeting.

Conclusions: Riliprubart reduced plasma-NfL levels by 31%; greater reductions correlated with higher INCAT response.

Author Disclosures: L. Querol: Received research grants from Instituto de Salud Carlos III – Ministry of Economy and Innovation (Spain), CIBERER, Fundació La Marató, GBS-CIDP Foundation International, UCB and Grifols. He received speaker or expert testimony honoraria from CSL Behring, Novartis, Sanofi, Merck, Annexon, Alnylam, Biogen, Janssen, Lundbeck, argenx, UCB, Dianthus, LFB, Avilar Therapeutics, Octapharma and Roche. He serves at Clinical Trial Steering Committee for Sanofi, and was Principal Investigator for UCB's CIDP01 trial. S. Hourcade, T. Chow, Y. Chen, M. Levit, T. R. Hammond, M. L. Kramer, N. Ternes, A. Seluzhytsky, M. Alonso-Alonso, N. Atassi: Employees of Sanofi and may hold shares and/or stock options in the company. R. A. Lewis: Consultant with Alexion; Annexon; Argenx; Avilar; BioCryst; Boehringer Ingleheim; CSL Behring; Dianthus; Grifols; Immunovant; Intellia; J&J; Nervosave; Nuvig; Sanofi; Seismic; Takeda. TGTX.

Acknowledgments: This Phase 2 trial (NCT04658472) is funded by Sanofi. The authors and Sanofi would like to thank the trial investigators, participants, and their families. The authors thank Xiaodong Luo, PhD, of Sanofi for providing statistical support for this trial. Medical writing support for original and this encore abstract was provided by Rachna Shukla, PhD and Shailaja Mahajan-Thakur, PhD, of Sanofi. We thank Renee Nguyen, PharmD, and Gerardo Gutierrez, PharmD, of Sanofi for contributions to the planning, review, and coordination of the abstract.

#1213 Givinostat Weight-Based Flexible Dosing: Rationale and Efficacy at the Different Doses

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Introduction: In the phase 3 EPIDYS study, patients with Duchenne muscular dystrophy received weight-based givinostat dosing plus standard of care (ie, corticosteroids), starting at dose A or B, depending on study protocol. Doses were adjusted (A to B or B to C) based on predefined rules related to tolerability to achieve the highest tolerated dose for each patient.

Objectives: To evaluate givinostat efficacy based on the final administered dose at week 72 (W72) in patients from EPIDYS.

Methods: Mean change from baseline (CFB) at W72 in 4-stair climb (4SC) time (seconds) and total North Star Ambulatory Assessment (NSAA) scores were analyzed.

Results: Thirty-nine patients started at dose A and 42 patients started at dose B. Dose was reduced in 36 patients. Overall, 21 patients received final dose A, 44 dose B, and 16 dose C. All patients had similar givinostat blood concentrations within the range considered efficacious throughout the study (5 samples/patient). At W72, the placebo-corrected difference in least squares (LS) mean CFB (95% CI) in 4SC time was A: −2.61 (−4.97, −0.26), B: −1.35 (−3.25, 0.54) and C: −1.90 (−4.48, 0.67). For NSAA, the LS mean CFB (placebo-corrected) was A: 3.35 (1.07, 5.64), B: 1.24 (−0.57, 3.05), and C: 1.94 (−0.58, 4.46).

Conclusions: Results numerically favored givinostat over placebo across all 3 doses. Flexible dosing enables the highest tolerated givinostat exposure for maximal efficacy while maintaining tolerability. Downtitration is feasible because all final doses yield comparable givinostat blood concentrations and clinically meaningful benefit.

#1211 Vastus lateralis fat fraction is associated with functional efficacy endpoints in patients with Duchenne muscular dystrophy treated with givinostat

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Introduction: Givinostat is an oral histone deacetylase inhibitor indicated for Duchenne muscular dystrophy (DMD) in patients aged ≥6 years. Vastus lateralis fat fraction (VLFF) is inversely correlated with daily activity and muscle functionality and predicts loss of function in patients with DMD. In the phase 3 EPIDYS study, givinostat treatment delayed fat infiltration compared with placebo (least squares mean difference: −2.92%; p=0.035) after 18 months.

Objective: To determine whether the change from baseline in VLFF is correlated with measures of disease progression in patients with DMD.

Methods: This post hoc analysis explored the relationship between VLFF and key efficacy endpoints observed at the end of study (month 18), including 4-stair climb (4SC), time to rise (TTR), 6-minute walking test (6MWT), and North Star Ambulatory Assessment (NSAA) in patients treated with givinostat (n=77) or placebo in addition to standard of care (ie, corticosteroids; n=37) from EPIDYS with baseline VLFF >5% and ≤30%.

Results: VLFF had a relatively high reciprocal correlation with 4SC (0.539, p=0.026), 6MWT (−0.528, p=0.029), and NSAA (−0.527, p=0.030). The correlation between VLFF and TTR (0.409, p=0.100) was not statistically significant.

Conclusions: Based on these results, the observed VLFF in response to treatment with givinostat suggests an association with efficacy endpoints evaluated in EPIDYS. These findings are consistent with previous studies showing a strong relationship between VLFF and functional measures and suggest that reductions in VLFF are clinically meaningful in patients treated with givinostat.

#1208 Givinostat Effect on Respiratory Function in Duchenne Muscular Dystrophy Before and After Ambulation Loss: Results From EPIDYS, LTSE, and PRO-DMD-01 Studies

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Introduction: Givinostat, an oral histone deacetylase inhibitor, is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients aged ≥6 years.

Objective: To evaluate the effect of givinostat on pulmonary function in patients who experienced loss of ambulation (LoA) during follow-up.

Methods: Data from the double-blind, randomized, phase 3 EPIDYS study in ambulant boys (aged ≥6 years) with DMD (NCT02851797) and its ongoing open-label extension (NCT03373968) were indirectly compared with PRO-DMD-01 (NCT01753804), a natural history study of DMD disease progression. Matching-adjusted indirect comparisons were used, adjusting for patient characteristics at LoA. Forced vital capacity (FVC) %–predicted mean trajectories before and after LoA were estimated using longitudinal mixed effects models.

Results: This analysis included 56 patients treated with givinostat and steroids compared with published data on 51 patients from the PRO-DMD-01 study who received steroids only. Among weighted givinostat-treated patients, 2 years before LoA, the weighted least squares mean (SE) FVC %–predicted was 91.3% (2.2%), decreasing to 83.0% (2.3%) at LoA and 74.4% (2.4%) 2 years post-LoA. The mean (SE) annual decline in FVC %–predicted was 3.6% (1.2%) before LoA and 3.9% (1.3%) after LoA. In the PRO-DMD-01 study, the mean (SE) annual decline in FVC %–predicted was 5.6% (2.1%) before LoA; this increased to 10.1% (2.2%) after LoA.

Conclusions: FVC%–predicted trajectories showed a slower and less pronounced decline in patients treated with givinostat compared with those treated with steroids only. These findings suggest improved pulmonary function stabilization with givinostat treatment.

#1207 Characterizing thrombocytopenia in patients with Duchenne muscular dystrophy treated with givinostat: results from the phase 3 EPIDYS trial

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Introduction: Thrombocytopenia is a known adverse event (AE) of givinostat, an oral histone deacetylase inhibitor indicated for Duchenne muscular dystrophy (DMD) treatment.

Objectives: To further characterize thrombocytopenia with givinostat treatment using data from the phase 3 EPIDYS trial (NCT02851797).

Methods: A total of 179 boys aged ≥6 years with DMD were assigned to oral givinostat (n=118) or placebo (n=61) over 18 months, while continuing systemic corticosteroids. The preferred AE terms of "thrombocytopenia" and "platelet count decreased" were assessed.

Results: Overall, 38 (32.2%) givinostat-treated patients experienced thrombocytopenia or decreased platelet count (AE terms aggregated) compared with 0 patients receiving placebo. All AEs of thrombocytopenia/decreased platelet count were grade 1 or 2 in severity, and none resulted in study drug withdrawal. A total of 17 (14.4%) and 16 (13.6%) givinostat-treated patients required dose reduction owing to thrombocytopenia or decreased platelet count, respectively. No events of thrombocytopenia or decreased platelet count led to temporary treatment interruption. The median (interquartile range [IQR]) time to platelet count nadir (first minimum value post baseline) with givinostat was 85.0 (41.0–254.0) days. The median (IQR) time to platelet count recovery (time from the minimum value < the lower limit of normal [n=62] to the first value within normal limits) was 26.0 (12.0–43.0) days.

Conclusions: With givinostat treatment, platelet count reductions occur early, and levels recover to normal within 1 month. Although thrombocytopenia/decreased platelet count resulted in dose reductions in 17 (14.4%) and 16 (13.6%) givinostat-treated patients, respectively, all events were mild or moderate in severity and managed without treatment interruption.

#1202 A Real-World Retrospective Cohort Study Characterizing Treatment Patterns Among Patients with MMN in the United States

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Introduction: Multifocal Motor Neuropathy (MMN) is a complement driven, rare immune-mediated motor neuropathy characterized by asymmetric limb weakness without sensory abnormalities, often resulting in significant disability. The treatment of MMN is challenged by delayed diagnosis due to symptom overlap with other conditions, treatment limited to intravenous immunoglobulin (IVIG), and barriers to access.

Objectives: This study aims to explore the treatment landscape for MMN using real-world data.

Methods: A retrospective cohort study was conducted using a US claims dataset (Komodo Health Jan 2016 – March 2024). Adult MMN patients were identified based on specified inclusion criteria and continuous enrollment one year pre-index date. Patients required ≥ 2 MMN ICD-10 diagnoses and ≥ 1 relevant test before the 2nd MMN diagnosis to be included for further analysis.

Results: We identified 330 MMN patients based on their most recent 12 months of data. Among them, 75% of patients received no therapy 1-year prior to diagnosis. We found that 31% of patients received IVIG in combination with steroids, 46% received IVIG alone, 3% received steroids alone and 20% received no therapy 1-year post-diagnosis. Finally, IVIG utilization was highest 1-year post-diagnosis, and decreased over time, from year 1 to year 3.

Conclusion: This study highlights potential gaps in the treatment of MMN, with a substantial proportion of patients receiving no therapy both before and after diagnosis. The findings highlight the dependence on IVIG, reveal the usage of steroids despite their ineffectiveness for MMN, and show a decrease in IVIG usage over time.

#1200 C1q Blockade with Tanruprubart Rapidly Attenuates Complement-Driven Acute Neuroinflammation and Accelerates Early Muscle Strength Recovery in Guillain–Barré Syndrome

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Introduction: Guillain-Barré syndrome (GBS) is characterized by classical complement pathway activation, neuroinflammation and nerve damage. Complement activation generates anaphylatoxins that elicit an acute cellular immune response including neutrophils and neutrophil degranulation, amplifying neuroinflammatory edema. Tanruprubart is a monoclonal antibody, targeting C1q, the classical complement pathway initiator. It was evaluated in a randomized, double-blind, placebo-controlled, Phase 3 trial in GBS (GBS-02; NCT04701164; N=214).

Objectives: This analysis evaluates the impact on complement-driven neutrophil activity in GBS.

Methods: Serum C1q levels were assessed over 26 weeks in the overall population, alongside serum neutrophil counts. Biomarkers of complement-mediated neuroinflammation were assessed in a subset. Efficacy measures included muscle strength (MRC sumscore).

Results: Following single administration of tanruprubart 30 mg/kg, circulating C1q was inhibited for approximately 1 week. Neutrophil counts, markers of neutrophil degranulation and activation, were elevated at baseline, consistent with an immunoinflammatory state. In the biomarker cohort (N=115), there was a treatment-induced reduction in neutrophil counts, neutrophil degranulation and activation markers as well as other pro-inflammatory signals, identified by gene ontology analysis at Week 1 ($p<0.0001$). This was mirrored by an improvement in muscle strength in tanruprubart 30 mg/kg-treated participants vs placebo (LS mean difference 8.2 points; 95% CI 3.28–13.14; $p<0.0029$, MRC sumscore).

Conclusions: Rapid and sustained blockade of C1q with tanruprubart provides a mechanistic link between complement inhibition, attenuation of acute neuroinflammation and early gains in muscle strength. These findings support the utility of biomarkers to objectively assess the therapeutic effect of a targeted immunotherapy in GBS

Disclosures: The study was sponsored by Annexon Biosciences (Brisbane, CA, USA).

HAK, PP, GM, PC	Employees and shareholders of Annexon Biosciences
CS	Consultancy/advisory role with Annexon Biosciences, argenx, CSL-Behring, Grifols, Kedrion, Sanofi, Takeda
QDM	Consultancy/advisory role with Annexon Biosciences
JN	Consultancy/advisory role with Annexon Biosciences
RG	Consultancy/advisory role with Annexon Biosciences
KAKA	No disclosures
ZI	Research funding from Fogarty International Center, National Institute of Neurological Disorders and Stroke of the National Institutes of Health, USA, and Annexon Biosciences

#1196 Early muscle strength improvements in patients with GBS treated with tanruprubart is a predictor of better outcomes

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Introduction: Guillain-Barré syndrome (GBS) is a complement-mediated, peripheral neuropathy characterized by rapidly progressive muscle weakness. In GBS-02, a double-blind, placebo-controlled, Phase 3 study (NCT04701164), tanruprubart (ANX005) 30 mg/kg single administration rapidly inhibited C1q, leading to early and sustained clinical improvements. The Medical Research Council sumscore (MRCss) at Week 1 is amongst the strongest predictors of prognosis in GBS and is a key component of the modified Erasmus GBS Outcome Score prognostic tool.

Objectives: This analysis evaluated whether improvement in MRCss at Week 1 predicts long-term functional outcomes.

Methods: We assessed correlation between MRCss (Least Squares [LS] mean change from baseline), GBS disability scale (GBS-DS), Overall Neuropathy Limitations Scale (ONLS), EQ-5D-5L and other outcomes using Kendall's tau estimates and Pearson. To estimate the extent changes in MRCss explain treatment effect, we applied proportional odds, logistic, and Cox regression models.

Results: At Week 1, tanruprubart 30 mg/kg rapidly improved muscle strength (MRCss LS mean difference 10.0 points, $p<0.0001$) vs placebo, with 86.1% of patients receiving tanruprubart improving ≥1 point vs 47.5% with placebo. Improvement in MRC was highly statistically correlated with better clinical outcomes including functional mobility (Timed-Up-and-Go, Rasch-built Overall Disability Scale, EQ-5D-5L Mobility), and reduced disability (GBS-DS, ONLS) from Week 1 through Week 26 ($p<0.0001$ for all comparisons).

Conclusions: These findings suggest that early muscle strength recovery measured by MRCss at Week 1 serves as a reliable indicator of overall treatment response in GBS. The rapid improvement observed with tanruprubart may reflect early reversal of conduction failure in largely intact motor neurons, contributing to better long-term functional outcomes.

Disclosures: The study was sponsored by Annexon Biosciences (Brisbane, CA, USA).

GM, H-AK, PC	Employees and shareholders of Annexon Biosciences
ZI	Research funding from Fogarty International Center, National Institute of Neurological Disorders and Stroke of the National Institutes of Health, USA, and Annexon Biosciences
KCG	Consultancy/advisory role with Annexon Biosciences, Argenx, Janssen, and Sanofi
KAKA	No relevant disclosures
JN	Consultancy/advisory role with Annexon Biosciences
QDM	Consultancy/advisory role with Annexon Biosciences

#1195 Targeted immunotherapy with tanruprubart reduces ventilation requirements in Guillain-Barré syndrome (GBS)

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Introduction: Guillain-Barré syndrome (GBS) is a neuromuscular emergency requiring hospitalization and often mechanical ventilation.

Objectives: A randomized, double-blind, placebo-controlled Phase 3 trial assessed tanruprubart (ANX005), a C1q inhibitor blocking classical complement activation, as a treatment for GBS, including its impact on duration of mechanical ventilation.

Methods: Duration of ventilation was analyzed with a zero-inflated negative binomial (ZINB) model to accommodate both the excess of zeroes (patients never ventilated) and the over dispersed counts among those ventilated. Two intercurrent events were prespecified: no ventilation and death. Those patients never requiring ventilation were assigned a ventilation duration of zero days, while the seven that died while ventilated were assigned the maximum trial length (182 days). The analysis was repeated without imputation for death and among patients already ventilated at treatment start with non-parametric methods.

Results: The median duration of ventilation amongst placebo-treated participants was 48 days. In the ZINB model both doses of tanruprubart showed significant reduction in median ventilation duration compared to placebo (28-day reduction, p=0.0356 for tanruprubart 30 mg/kg; 34-day reduction, p=0.0011 for tanruprubart 75 mg/kg). In the cohort of ventilated patients not imputed for death, median ventilation duration was reduced by 15 days for tanruprubart 30 mg/kg (p=0.0079) and 20 days for tanruprubart 75 mg/kg (p=0.0080) compared to placebo. Similar benefits were observed when analyses were restricted to patients already ventilated at treatment initiation.

Conclusions: Tanruprubart significantly reduces duration of mechanical ventilation in GBS, highlighting its potential to alleviate one of the critical burdens of severe GBS.

Disclosures: The study was sponsored by Annexon Biosciences (Brisbane, CA, USA).

H-AK, GM, PC	Employees and shareholders of Annexon Biosciences
QDM	Consultancy/advisory role with Annexon Biosciences
JN	Consultancy/advisory role with Annexon Biosciences
RG	Consultancy/advisory role with Annexon Biosciences
KAKA	No disclosures
ZI	Research funding from Fogarty International Center, National Institute of Neurological Disorders and Stroke of the National Institutes of Health, USA, and Annexon Biosciences
KCG	Consultancy/advisory role with Annexon Biosciences, Argenx, Janssen, and Sanofi

#1194 Safety and Efficacy of Riliprubart in CIDP: 76-week Phase 2 Trial Results

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Introduction: Riliprubart, a first-in-class humanized IgG4-monoclonal antibody, selectively inhibits activated-C1s in the classical-complement pathway and can be self-administrated subcutaneously via an auto-injector.

Objectives: To report efficacy and safety of riliprubart at W76.

Methods: This open-label, phase-2 trial (NCT04658472) evaluates riliprubart across three groups: SoC-Treated, SoC-Refractory, and SoC-Naïve. Participants undergo 24W treatment (Part-A), followed by optional treatment-extension (Part-B: W52). Primary endpoint (Part-A) is %-participants relapsing (SoC-Treated) or responding (SoC-Refractory/Naïve); ≥1-point change in adjusted INCAT disability score. Part-B evaluates safety and efficacy-durability based on %-relapse-free participants (SoC-Treated) or with sustained-response (SoC-Refractory/Naïve); no-increase in adjusted INCAT score ≥2-points at W76 relative to W24. Exploratory-endpoints include additional efficacy measures (INCAT, IRODS, MRC-SS, grip-strength), change in total-complement, and plasma neurofilament-light chain levels.

Results: As of August-2024, in SoC-Treated group, 81.3% (N=39/48) participants entered Part-B; 47.9% (N=23/48) completed Part-B (ongoing:27.1%; discontinued:6.3%). In SoC-Refractory and Naïve groups, 72.2% (N=13/18) and 50% (N=6/12) participants, respectively, entered Part-B, including 61.1% (N=11/18) in SoC-Refractory (ongoing:0%; discontinued:11.1%) and 16.7% (N=2/12) in SoC-Naïve group (ongoing:8.3%; discontinued:25%) completing Part-B. Updated full Part-B efficacy and safety data up to W76 will be presented at meeting.

Conclusions: Mature W76 results may suggest potential for riliprubart to demonstrate sustained clinical effect in participants who experience failure/inadequate response/residual disability despite SoC-therapy, supporting its development in phase-3, and potentially offering a new treatment option for CIDP.

Author Disclosures: L. Querol: Received research grants from Instituto de Salud Carlos III – Ministry of Economy and Innovation (Spain), CIBERER, Fundació La Marató, GBS-CIDP Foundation International, UCB and Grifols. He received speaker or expert testimony honoraria from CSL Behring, Novartis, Sanofi, Merck, Annexon, Alnylam, Biogen, Janssen, Lundbeck, argenx, UCB, Dianthus, LFB, Avilar Therapeutics, Octapharma and Roche. He serves at Clinical Trial Steering Committee for Sanofi and was Principal Investigator for UCB's CIDP01 trial. R. A. Lewis: Consultant with CSL Behring, BioCryst, Dianthus, Grifols, Nuvig, Pfizer, Sanofi (Steering Committee), Annexon,

Alexion, Avilar, argenx, Johnson & Johnson, Takeda, Boehringer Ingelheim (DSMB), Intellia (DSMB), Nervosave, TGTX, Seismic, and medical advisory board The GBS-CIDP Foundation International. He receives royalties from UptoDate and has been a speaker for Medscape. H-P. Hartung: Consultant with Sanofi and Octapharma. He has received fees for serving on Steering and Data Monitoring Committees from Biogen, BMS Celgene, GeNeuro, Merck, Novartis, Octapharma, Roche, and TG Therapeutics. P. A. van Doorn: Consultant with Annexon, argenx, Hansa Biopharma, Immunic, Octapharma, Roche, Sanofi (Institutional research fund received all honoraria), and received grants from the Prinses Beatrix Spierfonds, Sanquin, and Grifols. Jie Lin: Nothing to disclose. A. Dionne: Received honoraria from argenx and Alexion for conference and ad board. S. Attarian: Consultant with Alexion, argenx, UCB, Janssen, Hansa Biopharma, Roche, Sanofi, Amicus, LFB, Alnylam, Astrazeneca, Pfizer and Biogen. E. Wallstroem, K. Auwarter, Y. Lu, M. Alonso-Alonso, N. Atassi: Employees of Sanofi and may hold shares and/or stock options in the company. R. A. C. Hughes: Consultant with Hansa Biopharma, and Sanofi.

Acknowledgments: This Phase 2 trial (NCT04658472) is funded by Sanofi. The authors and Sanofi would like to thank the trial investigators, participants, and their families. The authors thank Xiaodong Luo, PhD, of Sanofi for providing statistical support for this trial. Statistical support was provided by Mannaig Girard, biostatistician from IT&M Stats, on behalf of Sanofi. Medical writing support for this original and encore abstract was provided by Kanupriya Gupta, PhD and Shailaja Mahajan-Thakur, PhD, of Sanofi. We thank Renee Nguyen, and Gerardo Gutierrez, PharmD, of Sanofi for contributions to the planning, review, and coordination of the original and encore abstract.

#1192 Riliprubart Phase 3 MOBILIZE and VITALIZE Trials for CIDP are Actively Enrolling Globally

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Introduction: Despite SoC therapies, people with CIDP may experience inadequate response. Riliprubart, a first-in-class, humanized IgG4-monoclonal antibody, selectively inhibits activated-C1s in the classical-complement pathway and can be self-administrated subcutaneously via an auto-injector. A phase-2 trial (NCT04658472) of treatment with riliprubart suggested promising clinical benefits at W24 with favorable benefit:risk profile.

Objective: To describe MOBILIZE and VITALIZE phase-3 trial designs/recruitment status.

Methods: MOBILIZE (NCT06290128), a randomized, double-blind, placebo-controlled trial, targets participants who failed/responded inadequately to SoC-Treatment (SoC-Refractory). VITALIZE (NCT06290141), a randomized, double-blind, double-dummy, non-inferiority/superiority design trial with sample size re-estimation, compares riliprubart vs. IVIg continuation in IVIg-Treated participants with residual disability. Both trials have W48 duration: W24 double-blind period (Part-A), then 24W open-label period (Part-B). In Part-A, participants are randomized (1:1) to receive riliprubart/placebo (MOBILIZE; N=up to 140), and riliprubart/IVIg (VITALIZE; N=up to 160). Eligible adults with CIDP (2021 EAN/PNS-guidelines) with INCAT-score 2-9 (score-2 exclusively from legs) are included. Primary-endpoints: %-participants responding (Part-A) (≥1-point decrease from baseline in adjusted INCAT-score) and long-term efficacy of riliprubart in adjusted INCAT-score (Part-B). Key secondary-endpoints: additional disability/impairment measures (Part-A)/long-term safety (Part-B).

Results: Both trials launched in 2024 and are actively enrolling participants across 28 countries in North/South America, Europe, and Asia.

Conclusions: These phase-3 trials represent innovations in the field by focusing on key unmet-needs (refractory disease/residual disability) with one trial having an active IVIg comparator.

Author disclosures: C. Sommer: Consultant for Algiax, Akigai, Grifols, Immunic, Kedrion, Sanofi, and Takeda, and has received honoraria for educational talks from Amicus, Alnylam, CSL Behring, Grifols, Kedrion, Orion, Pfizer, Takeda, and TEVA. L. Querol: Received research grants from Instituto de Salud Carlos III – Ministry of Economy and Innovation (Spain), CIBERER, Fundació La Marató, GBS-CIDP Foundation International, UCB and Grifols. He received speaker or expert testimony honoraria from CSL Behring, Novartis, Sanofi, Merck, Annexon, Alnylam, Biogen, Janssen, Lundbeck, argenx, UCB, Dianthus, LFB, Avilar Therapeutics, Octapharma and Roche. He serves at Clinical Trial Steering Committee for Sanofi, and was Principal Investigator for UCB's CIDP01 trial. J. Allen: Consultant for Sanofi, Alexion, Alnylam, argenx, Annexon, CSL Behring, Johnson & Johnson, Grifols, Takeda, Immunovant, Immunopharma, and Pfizer. I. S. J. Merkies: Received grants from Talecris Talents program, GBS-

CIDP Foundation International and FP7 EU program, outside the submitted work. A research foundation at the University of Maastricht received honoraria on behalf of him for participation in steering committees of the Talecris Immune Globulin Intravenous for Chronic Inflammatory Demyelinating Polyneuropathy Study, Commonwealth Serum Laboratories, Behring, Octapharma, LFB, Novartis, Union Chimique Belge, Johnson & Johnson, argenx, outside the submitted work, and Octapharma during the conduct of the study. P. A. van Doorn: Consultant with Annexon, argenx, Hansa Biopharma, Immunic, Octapharma, Roche, Sanofi, (Institutional research fund received all honoraria), and received grants from the Prinses Beatrix Spierfonds, Sanquin, and Grifols. E. Wallstroem, Y. Lu, L. Xiong, M. Alonso-Alonso, N. Atassi: Employees of Sanofi and may hold shares and/or stock options in the company. R. A. Lewis: Consultant with CSL Behring, BioCryst, Dianthus, Grifols, Nuvig, Pfizer, Sanofi (Steering Committee), Annexon, Alexion, Avilar, argenx, Johnson & Johnson, Takeda, Boehringer Ingelheim (DSMB), Intellia (DSMB), Nervosave, TGTX, Seismic, and medical advisory board for The GBS-CIDP Foundation International. He receives royalties from UptoDate and has been a speaker for Medscape.

Acknowledgements: These phase 3 trials are funded by Sanofi. The authors and Sanofi would like to thank the trial investigators, participants, and their families. The authors thank Xiaodong Luo, PhD, of Sanofi, for providing statistical support for this trial, and Beatrice Astruc, MD, on behalf of Sanofi, for her review. Medical writing support for original and this encore abstract was provided by Shailaja Mahajan-Thakur, PhD, and Kanupriya Gupta, PhD, of Sanofi. We thank Renee Nguyen, and Gerardo Gutierrez, PharmD, of Sanofi for contributions to the planning, review, and coordination of the original and encore abstract.

#1191 Efficacy of Riliprubart in Chronic Inflammatory Demyelinating Polyneuropathy: Phase 2 Subgroup Analyses

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Introduction: Riliprubart, a first-in-class humanized IgG4-monoclonal antibody, selectively inhibits activated-C1s in the classical complement pathway and can be self-administrated subcutaneously, via an auto-injector. In a Phase-2 trial (NCT04658472), riliprubart treatment showed favorable benefit:risk profile across a broad spectrum of participants with chronic inflammatory demyelinating polyneuropathy (CIDP).

Objectives: To report subgroup efficacy analyses from this ongoing trial.

Methods: This open-label, Phase-2 trial evaluates riliprubart across three groups: SoC-Treated, SoC-Refractory, and SoC-Naïve. Participants underwent 24W treatment (Part-A), followed by an optional treatment extension (Part-B: 52W). In Part-A, post-hoc analyses were performed in the SoC-Treated and SoC-Refractory groups, and all participants. Response rate for endpoints (INCAT, I-RODS, MRC-SS, grip strength) were evaluated in subgroups defined by standard demographics and clinical characteristics possibly predictive for the overall outcome (age, sex, CIDP subtype, time since start of therapy/diagnosis, previous therapies, Ig dose, baseline plasma NfL, and INCAT score).

Results: As of April-2024, preliminary interim data from 48 SoC-Treated and 18 SoC-Refractory participants (who completed or discontinued 24W treatment) were analyzed. In the overall population, the INCAT response rates were similar across all analyzed subgroups, indicating clinically meaningful benefits regardless of baseline characteristics. Consistent trends were observed across other efficacy measures. Available data of these results will be presented at the meeting.

Conclusions: The results suggest consistent clinical effects of riliprubart across a range of baseline characteristics and assessment scores for people living with CIDP who experience failure/inadequate response or residual disability despite SoC treatment.

Author Disclosures: R. A. Lewis: Consultant with CSL Behring, BioCryst, Dianthus, Grifols, Nuvig, Pfizer, Sanofi (Steering Committee), Annexon, Alexion, Avilar, argenx, Johnson & Johnson, Takeda, Boehringer Ingelheim (DSMB), Intellia (DSMB), Nervosave, TGTX, Seismic, and medical advisory board The GBS-CIDP Foundation International. He receives royalties from UptoDate and has been a speaker for Medscape. L. Querol: Received research grants

from Instituto de Salud Carlos III – Ministry of Economy and Innovation (Spain), CIBERER, Fundació La Marató, GBS-CIDP Foundation International, UCB and Grifols. He received speaker or expert testimony honoraria from CSL Behring, Novartis, Sanofi, Merck, Annexon, Alnylam, Biogen, Janssen, Lundbeck, argenx, UCB, Dianthus, LFB, Avilar Therapeutics, Octapharma and Roche. He serves at Clinical Trial Steering Committee for Sanofi and was Principal Investigator for UCB's CIDP01 trial. H-P. Hartung: Consultant with Sanofi and Octapharma. He has received fees for serving on Steering and Data Monitoring Committees from Biogen, BMS Celgene, GeNeuro, Merck, Novartis, Octapharma, Roche, and TG Therapeutics. P. A. van Doorn: Consultant with Annexon, argenx, Hansa Biopharma, Immunic, Octapharma, Roche, Sanofi (Institutional research fund received all honoraria), and received grants from the Prinses Beatrix Spierfonds, Sanquin, and Grifols. J. Lin: Nothing to disclose. A. Dionne: Received honoraria from argenx and Alexion for conference and ad board. S. Attarian: Consultant with Alexion, argenx, UCB, Janssen, Hansa Biopharma, Roche, Sanofi, Amicus, LFB, Alnylam, Astrazeneca, Pfizer and Biogen. E. Wallstroem, Y. Lu, M. Alonso-Alonso, N. Atassi: Employees of Sanofi and may hold shares and/or stock options in the company. R. A. C. Hughes: Consultant with Hansa Biopharma, and Sanofi.

Acknowledgments: This Phase 2 trial (NCT04658472) is funded by Sanofi. The authors and Sanofi would like to thank the trial investigators, participants, and their families. The authors thank Xiaodong Luo, PhD, of Sanofi for providing statistical support for this trial. Medical writing support for original abstract was provided by Kanupriya Gupta, PhD and Rachna Shukla, PhD of Sanofi. Editorial support for this encore abstract was provided by Preethi Bheereddy, MS (Pharm). We thank Renee Nguyen, and Gerardo Gutierrez, PharmD, of Sanofi for contributions to the planning, review, and coordination of the original and encore abstract.

#1186 Self-Administration of Rozanolixizumab in Patients With Generalised Myasthenia Gravis: The MG0020 Study

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Introduction: Rozanolixizumab is administered by healthcare professionals using programmable infusion pumps (IPs) for the treatment of adults with generalised myasthenia gravis (gMG). The Phase 3, open-label, crossover MG0020 study (NCT05681715) investigated patient self-administration of rozanolixizumab using manual push (MP) and IP methods.

Objectives: To assess successful self-administration, efficacy and safety of rozanolixizumab in MG0020.

Methods: Adults with gMG received once-weekly rozanolixizumab (weight-tiered dosing or 7 mg/kg) for 18 weeks: training (6 weeks) then 1:1 randomisation to Sequence 1 (IP then MP) or Sequence 2 (MP then IP) to self-administer (6 weeks per method). Primary endpoint: successful self-administration of rozanolixizumab (choosing correct infusion site, administering subcutaneously, delivering intended dose) at Weeks 12 and 18. Treatment-emergent adverse events (TEAEs) and change from baseline in total IgG and Myasthenia Gravis Activities of Daily Living (MG-ADL) score were also assessed.

Results: 62 patients received treatment; 55 were randomised to Sequence 1 (n=28) or Sequence 2 (n=27). Rozanolixizumab self-administration success rate was 100% with both methods at clinic and at home. Decreases from baseline in median total IgG and mean MG-ADL score were observed at Week 7 and maintained. TEAEs occurred in 75.8% (47/62) of patients; the most common TEAE was headache (21.0% [n=13]). Incidence of TEAEs was comparable for both methods (31.5% [n=17; IP] and 34.0% [n=18; MP]). Most TEAEs (97.6% [161/165 events]) were mild/moderate.

Conclusions: All patients successfully self-administered rozanolixizumab with both MP and IP. Efficacy and safety were consistent with the known profile, supporting MP or IP self-administration of rozanolixizumab in patients with gMG. Funding: UCB.

Disclosures: M. Isabel Leite is funded by the NHS (Myasthenia and Related Disorders Service and National Specialised Commissioning Group for Neuromyelitis Optica, UK) and by the University of Oxford, UK. She has been awarded research grants from UK associations for patients with myasthenia and with muscular disorders (Myaware and Muscular Dystrophy UK, respectively) and the University of Oxford. She has received speaker honoraria or travel grants from Biogen, the Guthy-Jackson Charitable Foundation, Novartis and UCB. She serves on scientific or educational advisory boards for argenx, Horizon Therapeutics (now Amgen) and UCB. Carlo Antozzi has received funding for congress and Institutional Review Board participation from Alexion Pharmaceuticals, argenx, Biogen, Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine), Momenta (now Johnson & Johnson)

and UCB. Tomasz Berkowicz and Artur Drużdż have nothing to disclose. Rachana K. Gandhi Mehta has received research funding from Akcea Pharmaceuticals (now AstraZeneca), EMD Serono, Novartis and UCB. She has served on advisory boards for Amgen and UCB and has received speaker honoraria from UCB. Zabeen K. Mahuwala has received compensation for advisory board participation from Alexion Pharmaceuticals and Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine) and has served as a panellist for Academic CME. She has received research funding for clinical trials paid to the University of Kentucky from Alexion Pharmaceuticals, argenx, Immunovant, Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine), RemeGen Biosciences and UCB. Jana Zschüntzsch has been awarded research grants from the German Innovationfond, German Society for Muscle Disease (DGM), and the Innovative Medicines Initiative 2 Joint Undertaking (IMI JU) of the European Commission (grant number: 101034427-2). She has received speaker honoraria or travel grants from Alexion, argenx, Kedrion, Roche and Sanofi. She serves on scientific or educational advisory boards for Alexion, Amicus, argenx, iThera, Kedrion, Sanofi, and UCB. She has received research support from argenx and UCB. She is a member of the European Reference Network for Rare Neuromuscular Diseases (ERN EURO-NMD) and a member of the medical advisory boards of the DGM and the German Myasthenia Gravis Society. Marion Boehnlein, Andreea Lavrov and Mark Morris are employees and shareholders of UCB. Puneet Singh is an employee and shareholder of UCB, and is a shareholder and previous employee of GSK. Vera Bril is a Consultant for Akcea, Alexion Pharmaceuticals, Alnylam, argenx, CSL, Grifols, Immunovant, Ionis, Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine), Momenta (now Johnson & Johnson), Novo Nordisk, Octapharma, Pfizer, Powell Mansfield, Roche, Sanofi, Takeda Pharmaceuticals and UCB. She has received research support from Akcea, Alexion Pharmaceuticals, argenx, CSL, Grifols, Immunovant, Ionis, Momenta (now Johnson & Johnson), Octapharma, Takeda Pharmaceuticals, UCB and Viela Bio (now Amgen).

#1184 Effect of Zilucoplan on Myasthenia Gravis-Specific Outcome Subdomain Scores in RAISE: A Phase 3 Study

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Introduction: In the Phase 3, double-blind RAISE study (NCT04115293), zilucoplan, a complement component 5 inhibitor, demonstrated clinically meaningful improvements versus placebo in adults with acetylcholine receptor autoantibody-positive generalised myasthenia gravis (gMG).

Objectives: To evaluate the effect of zilucoplan on Myasthenia Gravis Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis (QMG) subdomain scores (ocular, bulbar, respiratory and limb/axial muscle groups).

Methods: Patients were randomised to self-administer daily subcutaneous zilucoplan 0.3 mg/kg (n=86) or placebo (n=88) for 12 weeks. Primary endpoint: change from baseline (CFB) in MG-ADL total score at Week 12. This exploratory analysis assessed CFB in MG-ADL and QMG subdomain scores for patients with baseline score ≥1 in that subdomain.

Results: At Week 12, least squares mean (LSM) (95% CI) CFB in MG-ADL total score was: zilucoplan −4.39 (−5.28, −3.50) and placebo −2.30 (−3.17, −1.43); difference −2.09 (−3.24, −0.95); p=0.0004. LSM CFB in QMG total score was: zilucoplan −6.19 (−7.29, −5.08) and placebo −3.25 (−4.32, −2.17); difference −2.94 (−4.39, −1.49); p<0.0001. Mean (standard deviation [SD]) CFB in MG-ADL subdomain scores (zilucoplan vs placebo) was: ocular, −1.5 (1.7) vs −0.8 (1.6); bulbar, −1.9 (1.8) vs −1.1 (1.7); respiratory, −0.4 (0.6) vs −0.3 (0.7); limb/axial, −1.2 (1.5) vs −0.8 (1.4), respectively. Mean (SD) CFB in QMG subdomain scores was: ocular, −2.0 (2.1) vs −1.3 (2.2); bulbar, −1.6 (1.4) vs −1.1 (1.5); respiratory, −0.6 (0.7) vs −0.3 (0.8); limb/axial, −2.9 (2.6) vs −1.2 (2.4), respectively.

Conclusions: Zilucoplan treatment led to improvements relative to placebo across all subdomain scores in MG-ADL and QMG. Funding: UCB.

Disclosures: M. Isabel Leite is funded by the NHS (Myasthenia and Related Disorders Service and National Specialised Commissioning Group for Neuromyelitis Optica, UK) and by the University of Oxford, UK. She has been awarded research grants from UK associations for patients with myasthenia and with muscular disorders (Myaware and Muscular Dystrophy UK, respectively) and the University of Oxford. She has received speaker honoraria or travel grants from Biogen, the Guthy-Jackson Charitable Foundation, Novartis and UCB. She serves on scientific or educational advisory boards for argenx, Horizon Therapeutics (now Amgen) and UCB. Constantine Farmakidis

has received funding for medical advisory board participation from argenx, Johnson & Johnson and UCB and has served as a paid Consultant for the Muscular Dystrophy Association and UCB. Miriam Freimer has served as a paid Consultant for Arcellx, argenx and UCB. She receives research support from Abcuro, Alnylam Pharmaceuticals, argenx, Avidity Biosciences, COUR Pharmaceuticals, Dianthus Therapeutics, Fulcrum Therapeutics, Johnson & Johnson Innovative Medicine, the NIH, RemeGen Biosciences and UCB. Angela Genge has served as a paid Consultant for Alexion Pharmaceuticals, ALS Pharmaceuticals, Amicus Therapeutics, Amylyx Pharmaceuticals, Anelixis Pharmaceuticals, Annexon Biosciences, Apellis Pharmaceuticals, Atlantic Research Group, Biogen, Calico, Cytokinetics, Eli Lilly, Ionis Pharmaceuticals, Medtronic, Mitsubishi Tanabe Pharma, Orion, QurAlis, Ra Pharmaceuticals (now UCB), Roche, Sanofi Genzyme (now Sanofi), UCB and Wave Life Sciences. Channa Hewamadduma has received funding for consultancy on scientific or educational advisory boards for argenx, Biogen, Lupin, Roche and UCB, and has received an investigator-led research grant from UCB. His study activities were supported by a Sheffield NIHR BRC UK centre grant. He is a trustee of the myasthenia gravis patient organisation Myaware. Yessar Hussain was the RAISE Principal Investigator and has no financial disclosures. Angelina Maniaol has received payment for travel, meeting attendance, consulting honoraria or advisory board participation from Alexion Pharmaceuticals, argenx, Biogen, CSL Behring, Novartis and UCB. Kimiaki Utsugisawa has served as a paid Consultant for argenx, Chugai Pharmaceutical, HanAll Biopharma, Janssen Pharmaceuticals (now Johnson & Johnson Innovative Medicine), Merck, Mitsubishi Tanabe Pharma, UCB and Viela Bio (now Amgen); he has received speaker honoraria from Alexion Pharmaceuticals, argenx, the Japan Blood Products Organization and UCB. Tuan Vu is the USF Site Principal Investigator for MG clinical trials sponsored by Alexion/AstraZeneca Rare Disease, Amgen, argenx, Cartesian Therapeutics, COUR Pharmaceuticals, Dianthus Therapeutics, Immunovant, Johnson & Johnson, NMD Pharma, Regeneron Pharmaceuticals and UCB, and has served as a speaker for Alexion/AstraZeneca Rare Disease, argenx and CSL Behring. He has performed consulting work for Alexion/AstraZeneca Rare Disease, argenx, Dianthus Therapeutics and ImmunAbs. Michael D. Weiss has received honoraria for serving on scientific advisory boards for Alexion Pharmaceuticals, Amylyx Pharmaceuticals, argenx, Biogen, Immunovant, Mitsubishi Tanabe Pharma and Ra Pharmaceuticals (now UCB), consulting honoraria from CSL Behring and Cytokinetics, and speaker honoraria from Soleo Health. He also serves as a special government employee for the Food and Drug Administration. Babak Boroojerdi, Fiona Grimson and Natasa Savic are employees and shareholders of UCB. James F. Howard Jr. has received research support (paid to his institution) from Ad Scientiam, Alexion/AstraZeneca Rare Disease, argenx, Cartesian Therapeutics, the Centers for Disease Control and Prevention, the Muscular Dystrophy Association, the Myasthenia Gravis Foundation of America, the National Institutes of Health, NMD Pharma and UCB; has received honoraria/consulting fees from AcademicCME, Alexion/AstraZeneca Rare Disease, Amgen, argenx, Biohaven Ltd, Biologix Pharma, CheckRare CME, CorEvitas, Curie.Bio, Hansa Biopharma, Medscape CME, Merck EMD Serono, Novartis, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron Pharmaceuticals, Sanofi US, TG Therapeutics, Toleranzia AB and UCB; and has received non-financial support from Alexion/AstraZeneca Rare Disease, argenx, Biohaven Ltd, Cartesian Therapeutics, Toleranzia AB and UCB.

#1183 Safety and Efficacy Data From the Phase 2 ARDA Study of Empasiprubart in Multifocal Motor Neuropathy

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Introduction: Multifocal motor neuropathy (MMN) is a rare, immune-mediated, complement-driven, chronic neuropathy leading to axonal degeneration and progressive, disabling, asymmetric limb weakness. Empasiprubart binds C2, blocking classical and lectin complement pathways involved in MMN pathophysiology. In a neuropathy ex vivo mouse model, blocking C2 prevented neurofilament light protein (NfL) loss, maintaining axonal integrity. The phase 2 ARDA (NCT05225675) study assessed the safety and efficacy of empasiprubart in adults with MMN.

Methods: Enrolled participants had probable/definite MMN (2010 EFNS/PNS guidelines) and proven intravenous immunoglobulin (IVIg) dependency and were on a stable IVIg regimen before randomisation. Participants were assigned to 1 of 2 dosing cohorts, each randomised 2:1 to empasiprubart or placebo. Efficacy endpoints included IVIg retreatment rate, Patient Global Impression of Change scale score, change from baseline in grip strength (most affected hand), and serum NfL concentration in the double-blind treatment period.

Results: 27 participants (empasiprubart, n=18; placebo, n=9) were randomised per cohort. Participants in cohort 2 were older, with longer duration of disease and time since first IVIg treatment than those in cohort 1. Empasiprubart was well tolerated overall. Most adverse events were mild/moderate. Empasiprubart was associated with reduced IVIg retreatment risk vs placebo in both cohorts (Cohort 1 hazard ratio [95% confidence interval]: 0.09 [0.02; 0.44]; Cohort 2: 0.17 [0.02; 160]). Improvements in patients' self-assessment and grip strength were greater with empasiprubart vs placebo in both cohorts. NfL levels were low and decreased with empasiprubart treatment.

Conclusions: Efficacy and safety results from the ARDA trial support proof of concept of empasiprubart in MMN and pave the way for a phase 3 trial.

#1178 Long-Term Safety and Efficacy of Nipocalimab in Generalized Myasthenia Gravis: Vivacity-MG3 Open-Label Extension Phase Results

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Introduction: There is an unmet need for generalized myasthenia gravis (gMG) treatments that are safe and provide sustained symptom control for patients. In autoantibody-positive patients with gMG, nipocalimab, a novel neonatal Fc receptor (FcRn) blocker, demonstrated significant improvement from baseline over weeks 22, 23, 24 with mean (SE) change in MG-Activities of Daily Living (MG-ADL) score= −4.70 (0.329) vs. placebo (least square [LS] mean difference −1.45; p=0.002) in phase 3 Vivacity-MG3 study.

Objectives: To assess long-term safety and efficacy of nipocalimab in patients with gMG from the open-label extension (OLE) phase of Vivacity-MG3 (NCT04951622).

Methods: Autoantibody-positive (n=153, anti-acetylcholine receptor [AChR]/muscle-specific tyrosine kinase [MuSK]/low-density lipoprotein receptor [LRP4] positive) and triple-autoantibody-negative patients (n=43) with gMG (Myasthenia Gravis Foundation of America [MGFA] Class II-IV), inadequately controlled (MG-ADL >6) on standard-of-care (SOC) therapy, were randomized 1:1 to nipocalimab+SOC or placebo+SOC in a 24-week double-blind study, with option to enter ongoing OLE phase. Safety was assessed in patients receiving ≥1 dose of study drug.

Results: 137 autoantibody-positive patients from double-blind phase enrolled in OLE and received nipocalimab+SOC. Mean (SE) change in MG-ADL from double-blind baseline:= −5.73 (0.401) [n=81; OLE week 24]; −5.97 (0.681) [n=37; OLE week 48]. Nipocalimab was generally well-tolerated, with no new safety findings in OLE phase. Updated results of this ongoing study will be presented.

Conclusions: FcRn blocker nipocalimab demonstrated sustained disease control over 72 weeks across double-blind and open-label phases, as assessed using MG-ADL scale, in a broad population of autoantibody-positive patients with gMG in the phase 3 Vivacity-MG3 study.

Disclosures: Carlo Antozzi: Funding travel, meeting attendance & advisory board participation: Alexion, argenx, Momenta, Sanofi, UCB. Tuan Vu: Research or grant support: Alector, Alexion, AstraZeneca Rare Disease, Amylyx

Pharma, Annexon, Apellis, argenx, Biogen, CSL Behring, Cytokinetics, Dianthus, Harmony/Viela Bio, Healey Platform Trials, Mitsubishi Tanaka, RA/UCB, Sanofi, Momenta/Janssen, Woolsey Pharma; consultant &/or speaker bureau: Alexion, AstraZeneca Rare Disease, argenx, AbbVie, CSL Behring, Dianthus. Sindhu Ramchandren, Eriene Youssef, Panna Sanga, Keith Karcher, Yaowei Zhu, John Sheehan, and Hong Sun: Are/were employees of Johnson & Johnson; may hold stock or stock options in Johnson & Johnson. Richard J. Nowak: Research support: National Institutes of Health, Genentech, Inc., Alexion Pharmaceuticals, Inc., argenx, Annexon Biosciences, Inc., Ra Pharmaceuticals, Inc. (now UCB S.A.), the Myasthenia Gravis Foundation of America, Inc., Momenta Pharmaceuticals, Inc. (now Janssen), Immunovant, Inc., Grifols, S.A., and Viela Bio, Inc. (Horizon Therapeutics, now Amgen Inc.); consultant/advisor: Alexion Pharmaceuticals, Inc., argenx, Cabaletta Bio, Inc., Cour Pharmaceuticals, Ra Pharmaceuticals, Inc. (now UCB S.A.), Immunovant, Inc., Momenta Pharmaceuticals, Inc. (now Janssen), and Viela Bio, Inc. (Horizon Therapeutics, now Amgen Inc.). Constantine Farmakidis: Medical advisory board participation: Argenx, Janssen, UCB; Consulting: the Muscular Dystrophy Association. Vera Bril: Research support: argenx, Akcea, AZ-Alexion, CSL, Grifols, Immunovant, Ionis and Viela, Momenta (J&J), Octapharma, Takeda, UCB. Jan De Bleecker: Consultant: Alnylam Pharmaceuticals Inc, argenx, Alexion Pharmaceuticals Inc., CSL, Sanofi Genzyme, UCB. Huan Yang, Eduard Minks, Jin-Sung Park, Mariusz Grudniak, Marek Smilowski, and Kumaraswamy Sivakumar: No competing interests. Teresa Sevilla: Honoraria/attendance at advisory boards: argenx, UCB. Sarah Hoffmann: Speakers´ honoraria: Alexion, argenx, Grifols, Roche, UCB; honoraria/attendance at advisory boards: Alexion, argenx, Roche; member of the medical advisory board: the German Myasthenia Society, DMG. Marie Fitzgibbon: Employee of Johnson & Johnson; may own stock or stock options in Johnson & Johnson.

#1174 Characterization of the longer-term effectiveness of SMN-targeted therapies for spinal muscular atrophy: A systematic literature review

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Introduction: Approved SMA treatments include nusinersen, onasemnogene abeparvovec-xioi, and risdiplam. Although these provide significant clinical benefits, muscle weakness persists and remains an unmet need for patients with SMA.

Objectives: Using PubMed and Embase, we conducted a systematic literature review (SLR) to better understand and characterize the trajectory of longer-term outcomes with approved therapies.

Methods: The SLR included published works between 2017 and July 29, 2024, and was comprised of 18 clinical trials and 102 real-world studies. Each included motor assessments, such as the HFMSE (n=60), the RULM (n=50), or both (n=42), to evaluate treatment efficacy. Of the 978 articles identified, 120 met the search criteria. Here we focus on the nusinersen-related results, where mean change from baseline in HFMSE (n=17) and RULM (n=13) scores at ≥2 time points, with ≥1 assessment beyond 12mo, were reported.

Results: The longest follow-up study for nusinersen extended 7.6y and suggested a ceiling effect in motor function improvement around 2.5y, as measured by HFMSE. HFMSE scores fell below baseline around 6.7y; however, this decline occurred at a slower rate than would be expected in untreated patients. Motor function gains assessed by RULM showed rapid improvements within the first 2 to 3y, followed by a stable, sustained plateau.

Conclusions: SMA treatments are critical for motor neuron health; however, currently approved therapies leave notable residual disability and unmet need over the course of the disease. Additional treatment approaches are needed to address other aspects of the disease pathology to improve motor function outcomes.

#1172 Efficacy and safety of apitegromab in individuals with type 2 and type 3 spinal muscular atrophy evaluated in the phase 3 SAPPHIRE trial

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Introduction: Despite SMN-targeted therapy, individuals with SMA continue to experience progressive motor function loss.

Objectives: Assess safety and efficacy of apitegromab, a muscle-targeted therapy, in patients with nonambulatory SMA aged 2-21y receiving SMN-targeted therapy (nusinersen/risdiplam) enrolled in SAPPHIRE (NCT05156320), a double-blind, global, placebo-controlled Phase 3 trial.

Methods: Participants aged 2-12y were randomized 1:1:1 to receive apitegromab 20 (n=53) or 10mg/kg (n=53) or placebo (n=50) Q4W; those aged 13-21y were randomized 2:1 to receive apitegromab 20mg/kg (n=22) or placebo (n=10) Q4W. The primary efficacy endpoint was change from baseline (CFB) in HFMSE at 12mo. Secondary endpoints included RULM, proportion achieving HFMSE ≥3-point change, WHO motor development milestones, PK/PD, and safety.

Results: Overall, 188 participants enrolled (2-12y population, n=156; 13-21y population, n=32). The primary endpoint was achieved with statistically significant and clinically meaningful motor function improvements. At 12mo, least squares mean (LSM) difference (SE) in HFMSE CFB was 1.8 (0.76; P=0.0192) for the 2-12y population receiving apitegromab (combined dose) vs placebo. LSM (SE) difference in HFMSE CFB was 1.4 (0.88; P=0.1149) and 2.2 (0.87; nominal P=0.0121) for apitegromab 20 and 10mg/kg vs placebo, respectively. Total latent myostatin levels (PD) following apitegromab 20 and 10mg/kg were superimposable, suggesting target saturation. Efficacy was consistent across age groups; LSM difference in HFMSE CFB vs placebo was 1.8 for the 13-21y and pooled 2-21y populations. AEs were consistent with underlying disease and SMN-targeted therapy. No participants discontinued due to AEs.

Conclusions: Apitegromab provided significant and clinically meaningful improvements in motor function and was well-tolerated.

#1171 DYNE-101 targets the underlying cause of DM1 to enable multi-system functional improvement in the ACHIEVE trial

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Introduction: Myotonic dystrophy type 1 (DM1) is a spliceopathy that results in multi-system clinical manifestations. DYNE-101, an investigational therapeutic for the treatment of DM1, consists of a transferrin receptor 1-binding Fab conjugated to an ASO designed to target mutant nuclear DMPK RNA to correct splicing with the goal of enabling functional improvement.

Objectives: The safety and efficacy of DYNE-101 in adults with DM1 are being investigated in the Phase 1/2 ACHIEVE trial (NCT05481879).

Methods: In the 24-week placebo-controlled multiple ascending dose (MAD) portion of ACHIEVE, 56 participants received one of 5 dose/dose regimens of DYNE-101. All 56 participants have completed the MAD.

Results: At the dose selected for the registrational expansion cohort of ACHIEVE (6.8 mg/kg Q8W), DYNE-101 demonstrated robust total DMPK knockdown and splicing correction at 3 months. Correction in splicing was associated with early and robust functional improvement across multiple measures of muscle strength and function at 6 months, including vHOT (-38% mean change from baseline vs. +5% for placebo), QMT total score (+10.1% mean change from baseline vs. -3.9% for placebo), 10MWR (-7.2% mean change from baseline vs. +4.3% for placebo), and 5x STS (-12.4% mean change from baseline vs. +5.2% for placebo). Functional improvement with 6.8 mg/kg Q8W DYNE-101 was also noted in the MDHI total score, a patient reported outcome, including in CNS-related subscales. DYNE-101 had a favorable safety profile as of the data cut date.

Conclusions: Data from ACHIEVE suggest that DYNE-101 has a favorable safety profile and results in multi-system functional improvement in DM1.

#1165 MYASTHENIA GRAVIS EVENTS IN A RETROSPECTIVE UNITED STATES CLAIMS DATABASE STUDY

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Introduction: Myasthenia gravis (MG) is a rare autoantibody-mediated disease characterized by fatigability and fluctuating muscle weakness that may lead to exacerbations and MG crises.

Objectives: To characterize the incidence rate (IR) of serious MG exacerbations (ie, associated with hospitalization or emergency department visit), MG crises, and MG-related death among adults with MG over a 2-year period.

Methods: This retrospective cohort study used the anonymized Optum® Market Clarity claims dataset (2015-2018). Adult patients with ≥2 claims identified through MG ICD diagnostic codes were included. Further analyses were based on presence (prevalent) or absence (incident) of ≥1 MG diagnostic code and history of immunosuppressant use during the 1-year lookback period.

Results: A total of 5002 adults with MG (mean age, 61.94 years; 54% female; mean Charlson Comorbidity Index, 1.47) were included. IR (95% CI) of serious exacerbations was 19.12 (16.24-22.00)/1000 patient-years. Sixty-one patients had MG crises (IR=6.79 [5.09-8.50]/1000 patient-years), and 15 died due to MG exacerbation/crisis (IR=1.66 [0.82-2.50]/1000 patient-years). IR of serious exacerbations was higher in the older and more medically complex prevalent (n=2758) vs incident (n=2244) cohort. Patients with a history of immunosuppressant use (n=2215) were younger, more medically complex, and had higher rates of MG-related crisis and serious exacerbation compared with those without such history (n=2787).

Conclusions: This retrospective study confirmed that patients with MG continue to experience serious exacerbations and MG crises requiring medical attention, irrespective of treatment. These data support the need for more effective therapeutic strategies to minimize risk of such events early in the disease course.

Disclosures: JP and JG are employees of argenx. CW is a consultant with ZS associates. YL has served as a consultant for argenx, Amgen, and Vertex. TR has received honoraria for speaking and advice as well as travel support from argenx, Alexion, Celgene/BMS, Biogen, Johnson & Johnson, UCB, Roche, Sanofi Genzyme, Merck, Novartis, and Teva; and research funding from Alexion, argenx, Biogen, Novartis, Merck, Roche, Sanofi Genzyme, and SERB Pharmaceuticals.

#1163 Design of the first in human ArthemiR study, of a novel drug, ATX-01, for the treatment of DM1

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Introduction/Objectives: ATX-01 is a novel anti-microRNA in clinical development for the treatment of Myotonic Dystrophy. The objective of the current project was to design an efficient and feasible study to assess the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary clinical efficacy of ascending single and multiple doses of ATX-01 in participants with adult-onset Myotonic Dystrophy Type 1 (DM1).

Methods: The study design process was initiated based on non-clinical data, regulatory guidance, and latest knowledge of DM1 clinical trial design. The design was reviewed and modified based on feedback from patient groups, key opinion leaders in DM1, clinical study site staff, technical specialists, regulators, and external drug development experts. Learnings from other trials which preceded and are ongoing were incorporated.

Results: The ArthemiR Trial Design study protocol was approved in 6 countries (USA, Canada, UK, Spain, France and Italy). The design ensures that risks to participants are minimised, whilst optimising the design efficiency, balanced with feasibility. The first cohort of 8 participants has been dosed and the independent data safety monitoring board recommended proceeding to the second cohort as planned.

Conclusions: Best practices in study design include considerations of patient safety, data integrity and feasibility. It is critical to obtain and evaluate inputs from different sources before deciding on a final study design. These best practices provide a framework for future trials targeting rare diseases like DM1. Future phases will explore long-term efficacy and broader applications of ATX-01 in related conditions.

#1153 Clinical development of NMD670, a first-in-class, oral therapy targeting skeletal muscle in Charcot-Marie-Tooth disease, Myasthenia Gravis, and Spinal Muscular Atrophy

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Introduction: Failure of muscle activation due to compromised neuromuscular transmission is a common characteristic of neuromuscular disorders including Charcot-Marie-Tooth disease (CMT), myasthenia gravis (MG), and spinal muscular atrophy (SMA), and can contribute to symptoms of muscle weakness and fatigue. Therefore, therapies that facilitate muscle activation are promising candidates for treatment of these disorders. NMD670 is a first-in-class, muscle-targeted drug for enhancing muscle activation working via inhibition of the skeletal muscle specific chloride channel 1 (ClC-1). Preclinical studies demonstrated that NMD670 can improve muscle function in rodent models of CMT, MG, and SMA. The first-in-human single- and multiple-ascending dose trials with NMD670 demonstrated good tolerability and predictable pharmacokinetics. Additionally, a proof-of-mechanism trial of NMD670 in 12 MG patients demonstrated significant and clinically meaningful improvements of symptoms with a single dose.

Objectives: To further evaluate the safety and efficacy of NMD670, the clinical development is progressing in three randomized, placebo-controlled ph2 trials in CMT, MG, and SMA.

Methods: These trials test a twice daily dosing regimen of NMD670 over 21 days. The SYNAPSE-CMT trial is a proof-of-concept trial in ambulatory adults with CMT types 1 and 2. The SYNAPSE-MG trial is a dose-finding trial in AchR and MuSK antibody positive adults with MG. The SYNAPSE-SMA trial is a proof-of-concept trial in ambulatory adults with SMA type 3.

Results: N/A

Conclusions: Based on promising preclinical and clinical studies, the development of NMD670 is progressing in ph2 trials in CMT, MG, and SMA. Trial designs and enrolment updates will be presented at NMSG 2025.

#1148 Treatment of Post-COVID-19 POTS by inhibiting FcRn: A phase 2 randomized, placebo controlled, double-blind, proof of concept study with efgartigimod

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Introduction: Post–COVID-19 postural orthostatic tachycardia syndrome (POTS) is suspected to involve immune dysregulation, including the generation of autoantibodies against G-protein coupled receptors (GPCRs). These autoantibodies may act as partial agonists at adrenergic receptors, impairing peripheral vasomotor control and promoting sympathetic overactivity, which manifests as tachycardia without hypotension during orthostasis.

Objectives: We hypothesize that efgartigimod, an FcRn antagonist, will reduce circulating pathogenic IgG autoantibodies and lead to clinical improvement in individuals with post–COVID-19 POTS.

Methods: This is a phase II, randomized, double-blind, placebo-controlled, multicenter study evaluating the safety and efficacy of efgartigimod in adults with new-onset POTS following confirmed SARS-CoV-2 infection. Eligible participants must meet consensus diagnostic criteria for POTS and exhibit moderate to severe autonomic symptoms (COMPASS-31 ≥ 35). Approximately 42 participants will be randomized (2:1) to receive weekly intravenous infusions of efgartigimod or placebo for 24 weeks. Patients completing the double-blind phase may enter an open-label extension.

Results: Co-primary endpoints are the change from baseline to week 24 in COMPASS-31 and Malmo POTS Symptom Score, along with safety and tolerability. Secondary endpoints include measures of disease activity, fatigue, cognition, walking capacity, and quantitative autonomic testing. Exploratory endpoints include skin biopsy markers (intraepidermal nerve fiber density and sudomotor innervation) and peripheral blood biomarkers to investigate immunologic and histopathological correlates of treatment response.

Conclusions: This study will assess the therapeutic potential of FcRn inhibition in post–COVID-19 POTS and provide mechanistic insights into its autoimmune basis.
Funding: This study is sponsored by argenx

#1131 Interim Clinical Data Summary: A Phase 1b/2a Open-label, Dose Escalation Study to Evaluate the Safety and Clinical Activity of Intramuscular Doses of an AAV9-based gene therapy (BB-301) Administered to Subjects with Oculopharyngeal Muscular Dystrophy (OPMD) with Dysphagia

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Introduction/Objectives: OPMD is an autosomal-dominant degenerative muscle disorder characterized by progressive life-threatening dysphagia and ptosis which are caused by a mutation in the poly(A)-binding protein nuclear 1 (PABPN1) gene. No therapeutics are approved for use in OPMD. Current interventions are limited to palliative surgical procedures and dietary modifications, which do not address the underlying cause of disease.

Methods: BB-301, a novel investigational gene therapy designed to reduce the dysphagic symptom burden of OPMD, is being evaluated in a Phase 1b/2a, open-label dose escalation study (NCT06185673) to assess safety and clinical activity. Two drivers of dysphagic symptom burden are present in study subjects: post-swallow accumulation of food and liquid residue ("Total Pharyngeal Residue" or "TPR") or "inefficient swallowing", and incomplete pharyngeal rest post-swallow (i.e., pathologic sequential swallows characterized by the occurrence of involuntary contractions of the pharyngeal muscles without restoration of the resting pharyngeal diameter between contractions) or "ineffective swallowing". Outcome measures include videofluoroscopic swallowing studies for serial assessment of TPR and frequency of pathologic sequential swallowing, and the use of a patient-reported outcome instrument ("Sydney Swallow Questionnaire" or "SSQ"). Six subjects have been safely treated with the lowest-dose of BB-301.

Results/Conclusions: Interim study results for the first 3 subjects treated with BB-301 following 12-months, 12-months, and 3-months on treatment, respectively, demonstrate durable, clinically significant reductions in both causes of dysphagic symptoms and a reduction in SSQ Total Score, with 2 out of 3 subjects achieving a SSQ Total Score reflective of normal swallowing. There have been no severe adverse events in study subjects.

#1130 Efficacy and safety of autologous BCMA-directed mRNA CAR T-cell therapy in generalized myasthenia gravis: Results from a phase 2b randomized placebo-controlled trial

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Introduction: Descartes-08 is an autologous, BCMA-directed mRNA CAR T-cell therapy administered without chemotherapy. In a phase 1/2 study in generalized myasthenia gravis (gMG), six weekly outpatient infusions of Descartes-08 led to deep and durable improvements in MG severity.

Objectives: Assess effect of Descartes-08 versus placebo in adults with gMG measured by change in MG Composite (MGC) score from baseline to Month 3. Secondary endpoints included MG-ADL and other disease activity measures.

Methods: A phase 2b double-blind randomized placebo-controlled trial of Descartes-08 in adults with non-MuSK+ gMG requiring immunosuppression and baseline MG-ADL ≥6 (NCT04146051). Following leukapheresis and manufacturing of autologous products, participants were randomized 1:1. Primary endpoint was the proportion of participants achieving ≥5-point improvement in MGC at Month 3.

Results: Of 31 per-protocol participants (18 Descartes-08, 13 placebo), the median number of infusions received was six (range 2–6). At month 3, proportion of responders was significantly higher in the Descartes-08 arm in both overall population (67% versus 31%) and the AChR + population (64% versus 20%). Mean change in MGC was -5.6 (Descrartes-08) versus -0.5 (placebo) in the AChR+ and -5.4 versus -2.7 in the overall population. Mean changes in MG-ADL were -3.4 versus -0.9 (AChR+) and -3.8 versus -1.7 (overall). Most common adverse events reported in the Descartes-08 group were infusion-related reactions resolving within 48 hours.

Conclusions: Outpatient Descartes-08 administration was associated with significant reduction in disease activity scores compared to placebo with no concerning safety signals. A Phase 3 study is underway to further evaluate efficacy and safety.

#1218 Real-World Analysis of Age-Stratified Observed Adverse Clinical Outcomes in Duchenne Muscular Dystrophy Patients on Long-Term Glucocorticoid Therapy

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Introduction: Glucocorticoids (GCs) remain the gold standard for Duchenne Muscular Dystrophy (DMD) management, but long-term use is associated with adverse events (AEs) that vary by age.

Objectives: This study assessed the age-stratified prevalence of adverse outcomes across neurobehavioral, endocrine/metabolic, gastrointestinal, musculoskeletal, infectious and ophthalmologic categories among Medicaid patients on long-term GC therapy.

Methods: A retrospective analysis using 2016-2022 Medicaid T-MSIS Files identified male DMD patients aged ≤30 years with continuous enrollment. Long-term GC use was defined as ≥90 days with ≤60-day refill gaps. Age-stratified adverse outcome prevalence was assessed using ICD-10 codes.

Results: Among 1,365 patients (mean age: 12 years; 39% White, 27% Hispanic), most resided in California (17%), Texas (10%), and New York (9%). Mean GC duration was 2 years; 22% used Deflazacort only, 47% Prednisone only, and 31% used either medication at separate times. Multiple adverse outcomes increased with age, particularly in musculoskeletal, respiratory, and infection-related categories. Fractures peaked in the 8–13 age group (37%), while scoliosis (51%) and osteoporosis (50%) were highly prevalent overall, with rates rising gradually with age. Cataracts affected 9% of patients, increasing with age. Sleep apnea was the most prevalent outcome (62%), while anxiety-related disorders affected 22%; both peaked at ages 14-19 (73% and 27%, respectively). Upper respiratory infections affected 54% overall, while pneumonia (17%), septicemia (11%) and UTIs (8%) increased with age.

Conclusions: Observed adverse outcomes including neurobehavioral, metabolic, musculoskeletal and infectious complications, were highly prevalent and demonstrated age-related variations. These findings highlight the need for DMD therapies that mitigate AEs and slow disease progression.

#1199 Results of VBP15-006: a phase 2, open-label, multiple dose study of vamorolone in boys with DMD aged 2 to <4 and 7 to <18 years

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Introduction: Vamorolone, a novel corticosteroid (CS), is approved to treat boys with Duchenne muscular dystrophy (DMD) in the US, Europe, and UK.

Objectives: Confirm the safe and tolerable dose(s) of vamorolone for boys with DMD aged 2 to <4 and 7 to <18 years.

Methods: VBP15-006 was a phase 2, open-label, multiple-dose study in 54 patients with DMD. Those aged 2 to <4 years were CS-naïve and received vamorolone 2 mg/kg/day (d) (n=10) or 6 mg/kg/d (n=10). Those aged 7 to <18 years were either CS-naïve and received vamorolone 2 mg/kg/d (n=6) or 6 mg/kg/d (n=6), or CS-treated and received vamorolone 2 mg/kg/d (n=6) or 6 mg/kg/d (n=16).

Results: All participants completed the study. Median prior CS exposure in the age 7 to <18 years CS-treated boys was 54.1 months (vamorolone 2 mg/kg/d) and 93.1 months (vamorolone 6 mg/kg/d). Baseline comorbidities in CS-treated boys included fractures, cataracts, and psychiatric and endocrine disorders. At baseline, severe growth delay (median height percentile 1.6 [0.2; 16.8]) was reported for the age 7 to <18 years CS-treated boys allocated to receive vamorolone 6 mg/kg/d. Vamorolone showed dose-dependent pharmacokinetics at doses of 2–6 mg/kg/d, with maximum concentration reached within 2–4 hours and a half-life of 2 hours. Exposures were consistent with moderate variability at both doses after single and multiple dosing in both age groups. Dose-dependent increases in adverse events were seen across all age groups; none led to study discontinuation or death.

Conclusions: These results support the potential use of vamorolone across a broad age range in boys with DMD.

#1197 Vamorolone – the first novel corticosteroid with mineralocorticoid antagonist activity in man: evidence from LIONHEART and VBP15-004 biomarkers

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Introduction: Mineralocorticoid receptor antagonists (MRAs), eg, eplerenone, have proven beneficial in treating systolic heart failure and as a prophylactic cardioprotective treatment in Duchenne muscular dystrophy (DMD). It remains unknown whether vamorolone, a novel glucocorticoid receptor agonist, also exhibits MRA effects.

Objectives: To characterize the MRA effect of vamorolone in healthy volunteers and establish biomarkers of MRA activity in patients with DMD.

Methods: LIONHEART was a single-dose, open-label, randomized, 3-arm trial. MRA effect was assessed by changes in urine sodium to potassium (Na/K) ratio following fludrocortisone challenge. Thirty healthy male volunteers received vamorolone 20 mg/kg, eplerenone 200 mg, or no drug. Blood biomarkers for MRA activity were analyzed from the pivotal trial VBP15-004 in patients with DMD aged 4 to <7 years.

Results: In LIONHEART, both eplerenone and vamorolone effectively reversed the fludrocortisone-induced decrease in Na/K ratio (vamorolone vs no drug; $P<0.0001$). Vamorolone showed a significant natriuretic effect (magnitude similar to that of eplerenone), with no evidence of potassium retention. Both treatments were well tolerated. In VBP15-004, vamorolone 6 mg/kg (but not prednisone) increased serum renin, calcium, and phosphate, as well as the protein carriers of these inorganic ions (ASHG [Fetuin A], and Fetuin B), consistent with mineralocorticoid receptor antagonism. Two serum proteins involved in inorganic ion signaling via FGF23 pathways (Klotho, Anosmin-1) were also increased by vamorolone, but not by prednisone.

Conclusions: Taken together, these data confirm vamorolone as an MRA with potential reduced risk for clinically relevant hyperkalemia. Future research will evaluate its cardioprotective benefits in DMD.

Longitudinal Psychometric Properties of the Myotonic Dystrophy Health Index in a large multicentric cohort of people living with Myotonic Dystrophy Type 1.

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Introduction: The MDHI is a validated patient-reported outcome measure to assess disease burden in DM1. Although widely used in industry trials, further data on its longitudinal performance can enhance its interpretation in future studies.
Objectives: The aim of this study is to assess MDHI sensitivity to change and responsiveness.
Methods: Adult DM1 patients were enrolled in a 24-month longitudinal observational study (END-DM1). Confirmatory internal consistency and external validity were assessed. MDC was estimated using SEM and Esch, while MCID was calculated using anchor-based method based on the Domain Delta questionnaire. Sensitivity to change was analyzed through change scores; moreover, stratification into quartiles based on changes in MDHI total and short form (SF) scores was also performed to compare baseline subdomain scores and clinical variables, in order to identify predictors of disease burden trajectory. Responsiveness was assessed by comparing clinical outcomes across groups defined by MDHI score direction (improved/stable vs worsened).
Results: Of 451 DM1 patients assessed cross-sectionally, 147 completed 24-month follow-up. Internal consistency (Cronbach's $\alpha = 0.95$) and external validity were confirmed. MDC for total score was ±9.72 (SEM) and ±4.24 (ESch); subscale MDC ranged from ±12.62 to ±27.17 (SEM) and ±6.04 to ±12.70 (ESch). Quartile analysis showed baseline differences in specific subscales and motor/respiratory status among groups, suggesting predictive value. Changes in MDHI scores aligned with clinical outcomes, confirming responsiveness.
Conclusions: The MDHI shows strong longitudinal validity, sensitivity to change, and responsiveness in DM1. Specific subdomains and baseline motor/respiratory status may predict long-term burden, supporting MDHI's utility in clinical trials and natural history studies.