

## Pharmacological and Non-Pharmacological

### #812- Long-Term Safety, Tolerability, and Efficacy of Efgartigimod in Patients With Generalized Myasthenia Gravis: Concluding Analyses From the ADAPT+ Study

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**Introduction:** Efgartigimod, a human IgG1 antibody Fc-fragment, reduces total IgG (including pathogenic autoantibodies) through neonatal Fc receptor blockade.

**Objectives:** Evaluate long-term safety, tolerability, and efficacy of efgartigimod in generalized myasthenia gravis (gMG).

**Methods:** ADAPT, a 26-week, global, randomized, placebo-controlled, phase 3 trial, evaluated efgartigimod in adults with gMG; those completing ADAPT were eligible for the ADAPT+ open-label extension. Efgartigimod (10 mg/kg IV) was administered in cycles of once-weekly infusions for 4 weeks, with subsequent cycles initiated based on clinical evaluation. Primary objective was assessment of long-term safety and tolerability. Long-term efficacy was also assessed by Myasthenia Gravis Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis (QMG) scores.

**Results:** 90% (151/167) from ADAPT entered ADAPT+, and 145 (111 anti-AChR-Ab+/34 anti-AChR-Ab-) received  $\geq 1$  cycle by January 2022. With 229 patient-years of follow-up (mean duration per patient: 610 days), the most common AEs were headache (25%), COVID-19 (16%), nasopharyngitis (14%), diarrhea (10%), and urinary tract infection (9%), mostly mild-moderate and did not increase in frequency with subsequent cycles. AChR-Ab+ patients with  $\geq 1$  year follow-up across ADAPT/ADAPT+ (n=103) received median(range) 5.2(0.5-7.5) cycles/y. All anti-AChR-Ab+ patients (n=111) showed consistent, repeatable improvements in MG-ADL (mean[SE] change week 3, cycle 1: -5.0[0.33];  $\leq 11$  cycles) and QMG (-4.7[0.41];  $\leq 7$  cycles) during each cycle, mirroring repeatable reductions in total IgG (mean[SE] reduction, -55.9%[1.15];  $\leq 7$  cycles) and anti-AChR autoantibody levels (-56.1%[1.43]). AChR-Ab- patients experienced similar results.

**Conclusions:** Long-term efgartigimod treatment is well tolerated, resulting in consistent, repeatable improvements in clinical outcomes in adults with gMG.

## #813- Long-Term Safety, and Efficacy of Subcutaneous Efgartigimod PH20 in Patients With Generalized Myasthenia Gravis: Interim Results of ADAPT-SC+

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**Introduction:** In ADAPT-SC, subcutaneous (SC) efgartigimod PH20 (coformulated with recombinant human hyaluronidase PH20) demonstrated total IgG reduction noninferior at Day 29 to intravenous efgartigimod (approved in US and EU for AChR-Ab+ generalized myasthenia gravis [gMG], and in Japan regardless of antibody status), resulting in similar gMG improvement. Patients completing ADAPT-SC or enrolled in ADAPT+ could enroll in ongoing open-label extension ADAPT-SC+.

**Objectives:** Evaluate long-term safety, tolerability, and efficacy of efgartigimod PH20 SC in gMG.

**Methods:** Efgartigimod PH20 SC 1000 mg was administered in cycles of 4 weekly injections, with subsequent cycles initiated  $\geq 28$  days from last dose based on clinical evaluation. Clinical efficacy was assessed via Myasthenia Gravis Activities of Daily Living (MG-ADL). By March 2022, 164 participants received  $\geq 1$  dose of efgartigimod PH20 SC. Patients received approximately 3 cycles over a mean(SD) study duration of 170(59) days and 72 patient-years' observation.

**Results:** AEs were predominantly mild/moderate. The most frequent AEs were injection site erythema (25.6%), headache (15.2%), and COVID-19 (11.6%). Injection site reactions (ISRs) were mild/moderate and did not lead to treatment discontinuation. Most ISRs occurred within 24 hours and resolved spontaneously, with decreasing incidence in subsequent cycles. Two deaths occurred (metastatic renal cancer, COVID-19); neither were efgartigimod related per investigator. Consistent improvement from baseline in MG-ADL total score (mean[SE] improvement at week 4) was observed in cycles 1 (-4.0[0.25]), 2 (-3.8[0.29]), and 3 (-4.1[0.31]).

**Conclusions:** Multiple efgartigimod PH20 SC cycles were well tolerated with no new safety signals compared to ADAPT-SC. Safety and efficacy profiles were consistent with ADAPT/ADAPT+.

#798- Clinical-based prediction models for gastrostomy in patients with amyotrophic lateral sclerosis

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**Introduction:** Malnutrition and weight loss are negative prognostic factors for survival in patients living with amyotrophic lateral sclerosis (ALS). Dysphagia plays a prominent role and accelerate the disease. Early nutritional management is recommended but the exact time for placing gastrostomy is still debated.

**Objectives:** to identify the best easily collectable clinical variables to build a predictive model able to foresee the need for gastrostomy in ALS patients.

**Methods:** ALS patients followed at the NEMO Centre were retrospectively recruited. For each patient, anamnestic information and functional and nutritional assessment were identified and in order to predict the risk of PEG placement within 6 months from evaluation.

**Results:** A total of 263 ALS patients (median age of evaluation: 63.76 years [54.48 – 70.25], spinal/bulbar ratio of 2.25) were retrospectively recruited. Of these, 138 (52.47%) underwent a PEG placement within 6 months from evaluation, while 125 (47.53) did not. The Anamnestic Prediction Model (APM) resulted in a not well calibrated model (HL test,  $p=0.0117$ ), with fair discriminatory ability (c-index: 0.6943). The Anamnestic and Functional Prediction Model (A-FPM) resulted in a well calibrated model (HL test,  $p=0.5913$ ), with excellent discriminatory ability (c-index: 0.9063). The Anamnestic and Nutritional Prediction Model (A-NPM) resulted in a well calibrated model (HL test,  $p=0.4755$ ), with good discriminatory ability (c-index: 0.8074).

**Conclusions:** The models built and described in the present study, based on different clinical variables that might be easily recorded in a outpatient setting, might predict the time for gastrostomy and help clinicians in defining a specific patient-centered care plan.

## #796- MEND: MExiletine versus lamotrigine in Non-Dystrophic Myotonia

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**Introduction:** Non-dystrophic myotonias (NDM) are rare genetic neuromuscular disorders causing symptoms including stiffness. While there are currently no curative therapies, there are symptomatic treatments. Use of the gold standard therapy, mexiletine, can be limited in situations including cost restrictions, cardiac morbidity and pregnancy. A clinical trial has recently demonstrated efficacy of lamotrigine in NDM.

**Objectives:** We undertook a randomized, double-blind, cross-over trial to determine whether lamotrigine was not inferior to mexiletine. The primary outcome was a participant-reported stiffness severity score measured daily on a 0-9 scale and averaged over the last two weeks of each treatment period.

**Methods:** Patients were recruited via the National Hospital for Neurology and Neurosurgery Highly Specialised Services for Muscle Channelopathies. Participants were randomised to lamotrigine followed by mexiletine or mexiletine followed by lamotrigine. Each treatment period consisted of eight weeks with one-week washout in-between. Anti-myotonic treatments were washed out prior to commencement. The primary outcome was recorded daily using an IVR diary with email/phone check-ins. Adverse events were also recorded.

**Results:** Sixty participants were enrolled. A total of 14 participants (23%) withdrew due to loss to follow-up (n = 3), adverse events (n = 7), inability to consistently swallow trial capsules (n = 1), and inability to tolerate the up-titration protocol (n = 3). Analysis of primary outcome data is currently being undertaken. When taking Lamotrigine the primary outcome measure reduced from baseline by 2.83, while when taking Mexiletine a reduction from baseline by 3.32 was seen. Analysis of primary outcome data is currently being undertaken.

**Conclusions.** Further data analysis is ongoing and results will be presented at the NMSG meeting.

## #741- Investing to Save: Evaluation of Unplanned Hospital Admissions of Neuromuscular Patients in Greater Manchester, UK.

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**Background:** Unplanned hospital admissions for people with neuromuscular diseases (pwNMDs) are associated with morbidity, mortality, and carry financial implications for the healthcare system. Such admissions may be avoidable, and frequency influenced by the quality of routine care services.

**Objectives:** To examine the characteristics of unplanned admissions of pwNMDs in Greater Manchester, and investigate factors associated with their occurrence.

**Methods:** Retrospective case-note evaluation of 97 randomly selected pwNMD and their corresponding 120 unplanned admissions to the Northern Care Alliance NHS Foundation Trust 2017-2019. Potential preventability and predisposing factors for each admission were assessed.

**Results:** At first admission, 56.7% (55/97) of patients had a prior NMD diagnosis, while only 21.6% (21/97) were known to a NM service. Of the 78.4% (76/97) patients not known to NM services, 44.7% (34/76) had a prior NMD diagnosis at first admission. Of all 120 admissions, 35.8% (43/120) were potentially preventable. Of the 63 admissions related to the underlying NMD, 55.6% (35/63) were potentially preventable. The most frequent cause for preventability was admission for a known potentially preventable complication of NMD. The median length of stay was 4 and 6 days, for total (n=120) and potentially preventable (n=43) admissions respectively. A delayed discharge was recorded in 28% (12/43) of potentially preventable admissions. No emergency plans were found in the notes for any patient.

**Conclusions:** A significant burden of potentially preventable unplanned admissions of pwNMDs were identified. Improvements in the routine provision of long-term care for these patients could reduce this risk and improve outcomes.

#764- Development of prediction models based on respiratory assessments to determine the need for Non-Invasive Ventilation in patients with Myotonic Dystrophy type 1.

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**ABSTRACT**

**Introduction:** Myotonic dystrophy type 1 (DM1) is a slowly progressive, multisystem, autosomal dominant disorder, in which the impairments of respiratory systems representing one of the main causes of death.

**Objective:** The aim of our study was to develop prediction models to identify the most appropriate test(s) providing indication for NIV.

**Methods:** DM1 patients attending the NEMO Clinical Center (Milan) between January 2008 and July 2020, who had been subjected to a complete battery of respiratory tests were retrospectively recruited. Demographic, clinical and anthropometric characteristics were collected, as well as arterial blood gas analysis, spirometry, respiratory muscle strength, cough efficacy and nocturnal oximetry as respiratory assessments. Patients were stratified in those requiring NIV and those with normal respiratory function.

**Results:** Out of 151 DM1 patients (median age: 44yrs [35.00 – 53.00], male/female ratio: 0.80 (67/84)), 76 had an indication for NIV initiation (50.33%). ABG, spirometry and nocturnal oximetry prediction models resulted in an excellent discriminatory ability in distinguishing patients who needed NIV from those who did not (AUC of 0.818, 0.808 and 0.935; respectively). An easy-to-use calculator was developed to automatically determine a score of NIV necessity based on the prediction equations generated from each aforementioned prediction model.

**Conclusions:** The proposed prediction models may help to identify which patients are at a higher risk of requiring ventilator support and therefore help in defining individual management plans and criteria for specific interventions early in the disease course. As future steps, although internally validated, an external validation of the proposed prediction models will be necessary to evaluate their generalizability.

#746 A UK experience of symptomatic treatment of myotonia with Lamotrigine

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**Introduction:** Lamotrigine has recently been shown to be effective for symptomatic treatment for non-dystrophic myotonia; little data on real-world clinical experience exists.

**Objectives:** To report our clinical experience of using Lamotrigine for treatment using the Myotonia-Behaviour-Score (MBS) in patients with myotonia.

**Methods:** We retrospectively evaluated the MBS from a UK single-centre of patients attending the Nationally Commissioned Highly Specialised Service for Channelopathies. The MBS was collected at pre treatment, six months follow up and after the highest dose increase was reached.

**Results:** Out of 26 patients on Lamotrigine, 12 were evaluated to date. Of those half (6) had *CLCN1* mutations and other half (6) *SCN4A* mutations, with mean (SD) age of 43.4 (15.6) years. Mean reduction in MBS of seven patients after six months of treatment was from 3.6 to 1.7, which was statistically significant ( $p=0.0176$ ). There was no significant difference in MBS reduction in five patients with average treatment duration of 2.4 ( $\pm 1.3$ ) (range 1-3.7) years after the highest dose increase (range 3 to 1.8,  $p=0.2$ ). One patient experienced nausea, which ceased after stopping the medication.

**Conclusions:** These preliminary data suggest that treatment with Lamotrigine effectively reduce myotonia in selected patients with non-dystrophic myotonia. Further data analysis is ongoing.

## #750 Safety and efficacy of ataluren in nmDMD patients from Study 041, a phase 3, randomized, double-blind, placebo-controlled trial

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**Introduction:** Study 041 (NCT03179631) is a phase 3, double-blind, placebo-controlled 72-week ataluren trial in nonsense mutation Duchenne muscular dystrophy (nmDMD) patients followed by a 72-week open-label period.

**Objectives:** To describe efficacy and safety results from the placebo-controlled phase.

**Methods:** Boys with nmDMD aged  $\geq 5$  years, on corticosteroids, and with a 6-minute walk distance (6MWD)  $\geq 150$ m were eligible. The primary objective was to determine ataluren's effect on ambulatory function, assessed by the 6-minute walk test. Boys were randomized 1:1 to ataluren:placebo. The intention-to-treat (ITT) population comprised randomized boys who received  $\geq 1$  dose of study treatment. Predefined subgroups included boys with  $\geq 300$ m 6MWD and  $\geq 5$ s stand from supine (primary) and those with 300-400m 6MWD.

**Results:** Ataluren and placebo groups in the ITT population and key subgroups were balanced according to enrolment age, baseline 6MWD, corticosteroid use and time to stand from supine. Significant differences in mean 6MWD change from baseline and rate of change favored ataluren in the ITT population (14.4m; 0.20m/week;  $p=0.0248$ ) and 300-400m 6MWD subgroup (24.2m; 0.34m/week;  $p=0.0310$ ), representing a 21% and 30% slowing of the decline rate in 6MWD in these groups, respectively. There were significant treatment benefits in time to 10% worsening of 6MWD. The number of ITT patients who lost ambulation receiving placebo was almost double of those receiving ataluren. Ataluren was well tolerated, had no probable drug-related serious adverse events (AEs), and AE frequency (85.3%) was similar to placebo (84.7%).

**Conclusions:** Study 041 confirms ataluren's favorable risk-benefit as shown in previous clinical and real-world evidence studies.



## #752 Ataluren preserves upper limb function in nmDMD patients from Study 041, a phase 3 placebo-controlled trial, and the STRIDE Registry

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**Introduction:** Study 041 (NCT03179631) is a phase 3, double-blind, placebo-controlled 72-week ataluren trial in nonsense mutation Duchenne muscular dystrophy (nmDMD) patients. The STRIDE Registry (NCT02369731) is an ongoing, long-term, real-world evidence study.

**Objectives:** To assess performance of upper limb (PUL) function in nmDMD patients receiving ataluren+standard of care (SoC).

**Methods:** In Study 041, nmDMD boys aged  $\geq 5$  years, on stable corticosteroid regimen, and with 6-minute walk distance (6MWD)  $\geq 150$ m were randomized 1:1, ataluren:placebo. The intention-to-treat (ITT) population comprised randomized boys who received at least one dose of study treatment (N=359; mean age 8.1 years); baseline 300-400m 6MWD (n=169) was a key subgroup. STRIDE patients were propensity-score matched to patients receiving SoC alone in CINRG DNHS (NCT00468832), yielding a comparable population (N=261). Kaplan-Meier analyses estimated age at loss of upper limb function.

**Results:** Least-squares mean PUL total score change from baseline to week 72 (by MMRM analysis) numerically favored ataluren vs placebo (0.44,  $p=0.1059$ ) in the Study 041 ITT population and was significant in the 300–400m 6MWD subgroup (1.02,  $p=0.0165$ ).

In matched STRIDE vs CINRG patients (mean last assessment age, 13.1 vs 14.6), ataluren preserved hand-to-mouth function by 3.4 years ( $p=0.0046$ ) as assessed by entry level items of PUL vs Brooke Scale, respectively. Median age at loss of overhead reach numerically favored STRIDE, consistent with the overall trend (15.8 vs 12.6;  $p=0.2872$ ). Median age at loss of distal hand function was non-estimable for STRIDE patients.

**Conclusions:** Results indicate that ataluren may help preserve upper limb function in advanced nmDMD patients.

#756 A Phase 1/2 Study of DYNE-251 in Males with DMD Mutations Amenable to Exon 51 Skipping: DELIVER Study Design

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**Background:** Approved therapies for Duchenne muscular dystrophy (DMD) use exon skipping phosphorodiamidate morpholino oligomers (PMOs) that enable the translation of a shortened, functional dystrophin protein, but their success has been hampered by poor muscle delivery and uptake. DYNE-251 is an exon 51 skipping PMO conjugated to an antigen-binding fragment targeting the transferrin receptor 1 (TfR1) which is expressed on muscle. Robust preclinical data have supported the clinical development of DYNE-251 for the treatment of DMD.

**Objectives:** To evaluate the safety, tolerability, and dystrophin levels in muscle following treatment with DYNE-251.

**Methods:** DELIVER is an ongoing randomized, double-blind, placebo-controlled, multiple ascending dose (MAD) study of DYNE-251 administered intravenously to ambulant and non-ambulant males (4-16 years) with exon 51 skip-amenable mutations (NCT05524883). The study consists of a MAD/placebo-controlled period (24 weeks), open-label extension (OLE, 24 weeks), and long-term extension (LTE) period (96 weeks). Primary outcomes are the number of participants with treatment-emergent adverse events and the change from baseline in dystrophin levels in muscle at Week 25.

**Results:** The DELIVER trial is expected to enroll ~48 males across 7 cohorts – 0.7, 1.4, 2.8, 5, 10, 20, and 40 mg/kg approximate PMO equivalent doses of DYNE-251. Participants will be randomized in a 2:1 or in a 3:1 ratio of DYNE-251 to placebo administered every 4 weeks during the MAD/placebo-controlled period. All participants will receive the highest safe and tolerable dose during the OLE and LTE periods.

**Conclusions:** Initial data from the MAD portion of the study are expected in H2 2023.

#757 A Phase 1/2 Randomized, Placebo-Controlled, Multiple Ascending Dose Study (ACHIEVE) of DYNE-101 in Individuals with Myotonic Dystrophy Type 1 (DM1)

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**Introduction:** Myotonic dystrophy type 1 (DM1) is caused by expansion of CUG repeats in the dystrophin myotonia protein kinase (*DMPK*) RNA which sequester splicing regulators into toxic nuclear foci, leading to a spliceopathy that drives DM1 clinical manifestations. DYNE-101 is a transferrin receptor (TfR)1-targeting antigen-binding fragment conjugated to a gapmer antisense oligonucleotide (ASO) that targets nuclear *DMPK* RNA. Preclinical data show that DYNE-101 reduces mutant *DMPK* RNA, foci formation, and corrects splicing, suggesting a potential effect in individuals with DM1. DYNE-101 was well-tolerated in non-human primates.

**Objectives:** To evaluate the safety, tolerability, pharmacodynamics, efficacy, and pharmacokinetics of DYNE-101 administered intravenously to adults with DM1 aged 18-49 years.

**Methods:** ACHIEVE is an ongoing, randomized, double-blinded, placebo-controlled, multiple ascending dose (MAD) Phase 1/2 trial (NCT05481879). The primary outcome is the number of participants with treatment-emergent adverse events. Change from baseline in splicing index in skeletal muscle assessed by biopsies at baseline, 12, and 24 weeks is a secondary outcome.

**Results:** The study will enroll ~72 participants in 4 cohorts of ascending doses of DYNE-101 (1.8, 3.4, 6.8, and 10.2 mg/kg approximate ASO-equivalent doses). Participants who receive 1.8 mg/kg DYNE-101 will be dosed every 4 weeks. Participants who receive 3.4, 6.8, and 10.2 mg/kg DYNE-101 will be dosed every 4 or 8 weeks. All participants will receive the highest safe and tolerable dose of DYNE-101 during the subsequent 24-week open-label and 96-week long-term extension periods.

**Conclusions:** Initial safety, tolerability, and splicing data from the MAD portion are expected in H2 2023.

## #780 FREEDOM-DM1: Phase 1 Study to Assess Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of PGN-EDODM1 in Adults with Myotonic Dystrophy Type 1 (DM1)

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**Introduction:** PepGen's enhanced delivery oligonucleotide cell-penetrating peptide technology is engineered to optimize tissue delivery and cellular uptake of therapeutic oligonucleotides. PGN-EDODM1 is being developed for the treatment of myotonic dystrophy type 1 (DM1). PGN-EDODM1 is designed to bind to pathogenic CUG trinucleotide repeat expansion in *DMPK* mRNA, thereby liberating MBNL1 protein through steric blocking and without degrading *DMPK* transcript. The release of MBNL1 protein is hypothesized to correct DM1 spliceopathy, the root cause of DM1 pathology. Nonclinical data demonstrated that PGN-EDODM1 reduced the number of myonuclear foci (DM1 cells), liberated MBNL1 (DM1 cells), corrected mis-splicing (DM1 cells, HSA<sup>LR</sup> mouse) and normalized myotonia (HSA<sup>LR</sup> mouse).

**Objectives:** Evaluate the safety and tolerability (primary objective) and plasma pharmacokinetics (secondary objective) following a single dose of PGN-EDODM1 in adults living with DM1. Exploratory objectives include the concentration of PGN-EDODM1 in skeletal muscle, pharmacodynamics (changes in the splicing pattern of affected transcripts), pharmacokinetics in urine, and functional measures (including video hand opening time to assess myotonia) to inform future studies.

**Methods:** Males and females 18-50 years of age, inclusive, with genetically confirmed diagnosis of DM1 will be randomized 3:1 (6 PGN-EDODM1 and 2 placebo) in each dose cohort. A muscle needle biopsy (tibialis anterior) will be performed at baseline, Week 4, and Week 16 for measurement of tissue drug concentrations and splicing of selected transcripts.

**Conclusion:** The Phase 1 study FREEDOM-DM1 will evaluate the continued development of PGN-EDODM1 for the treatment of the root cause of DM1. The study design of FREEDOM-DM1 will be presented.

## #781 CONNECT-EDO51: Nonclinical and Phase 1 Data Support Phase 2 Trial Designs to Continue Evaluating Safety and Efficacy of PGN-EDO51 for Duchenne Muscular Dystrophy (DMD) Amenable to Exon 51 Skipping

Jane Larkindale, Sarah Vacca, Jennifer Shoskes, Jaya Goyal, Pallavi Lonkar, Ashling Holland, Jeffrey Foy, Brijesh Garg, Shaoxia Yu, Michelle Mellion

(PepGen Inc., Boston, MA)

**Introduction:** PepGen's enhanced delivery oligonucleotide cell-penetrating peptide technology is engineered to optimize tissue delivery and cellular uptake of therapeutic oligonucleotides. PGN-EDO51 is being evaluated for the treatment of DMD amenable to exon 51 skipping.

**Objectives:** Evaluate efficacy (exon skipping and dystrophin production), safety, and tolerability of PGN-EDO51 in people with DMD.

**Methods:** Nonclinical studies and a Phase 1 single-dose study in healthy adult male volunteers (HVs) informed the design of Phase 2 studies.

**Results:** A single dose of 15 mg/kg PGN-EDO51 in HVs attained the highest published levels of oligonucleotide (50nM) and exon skipping (2% skipping, ddPCR) in biceps reported after a single dose in HVs and that were sustained up to 28 days postdose. PGN-EDO51 was generally well tolerated. In monkeys, a single 20 mg/kg dose resulted in similar exon skipping levels in the biceps (2.5%, ddPCR); and four repeat monthly doses (20 mg/kg) showed accumulation of exon skipped transcripts (34.9% skipping, ddPCR): a 14-fold increase compared to single doses. In *mdx* mice, exon skipping and dystrophin were observed 4 weeks after a single 30 mg/kg dose of PGN-EDO23 (murine analogue); and four repeat monthly doses resulted in 91.5% exon skipping (RT-PCR) and 82.3% dystrophin.

**Conclusions:** The data support that monthly repeat PGN-EDO51 dosing may result in the accumulation of skipped transcripts and dystrophin protein. Two Phase 2 clinical studies will assess the safety and efficacy of repeat doses of PGN-EDO51 in males living with DMD amenable to exon 51 skipping: CONNECT1-EDO51 is an open-label trial in Canada; CONNECT2-EDO51 is a multinational, randomized placebo-controlled trial. Study designs will be presented.

## #792 Phase 3b Extension Study Evaluating Superiority of Daily vs Approved On/Off Oral Edaravone Dosing in Patients With Amyotrophic Lateral Sclerosis

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**Introduction:** Intravenous edaravone (Radicava<sup>®</sup>/Radicut) was shown to slow the rate of physical functional decline in amyotrophic lateral sclerosis (ALS). Oral edaravone (Radicava ORS<sup>®</sup> [edaravone] oral suspension) was approved by the US Food and Drug Administration for use in patients with ALS in May 2022 and has since gained approval in Canada, Japan, and Switzerland.

**Objectives:** Study MT-1186-A04 (NCT05151471) is an ongoing, multicenter, phase 3b, double-blind, parallel group, randomized extension study evaluating and comparing the long-term safety, efficacy, and tolerability of 2 oral edaravone dosing regimens for up to an additional 48 weeks following the end of Study MT-1186-A02 in patients with ALS, comprising a total duration of up to 96 weeks.

**Methods:** Study MT-1186-A04 will evaluate 2 oral edaravone dosing regimens (105-mg dose). Group 1 will have oral edaravone administered once daily for each 28-day cycle. Group 2 will have oral edaravone administered for 10 days followed by placebo for 18 days in each 28-day cycle. Dosing in both groups will continue up to 48 weeks. Study MT-1186-A04 is anticipated to include approximately 300 adult patients who have completed Study MT-1186-A02. The primary objective is to evaluate the efficacy of each dosing regimen based on the randomization date in Study MT-1186-A02 to at least a 12-point Revised ALS Functional Rating Score decrease or death, whichever happens first, over the course of the study.

**Results:** Ongoing.

**Conclusions:** This extension study will provide important information on the safety, efficacy, and tolerability of 2 oral edaravone dosing regimens in patients with ALS.

**Sponsorship:** Mitsubishi Tanabe Pharma America, Inc.

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**Disclosure:**

JR is a consultant for Expansion Therapeutics, National Institutes of Health, Department of Defense, F Prime, The ALS Association. SD and MC have nothing to disclose. LZ has received honoraria for consulting with

## Abstracts from the 2023 Neuromuscular Study Group Meeting

MTP, Biogen, Amylyx and Cytokinetics. AC serves on scientific advisory boards for Mitsubishi Tanabe, Roche, Biogen, Denali Pharma, AC Immune, Biogen, Lilly, and Cytokinetics and has received a research grant from Biogen. ACL has served as a scientific consultant for Mitsubishi Tanabe Pharma America, Inc. GS has served as a medical advisor for Mitsubishi Tanabe Pharma Corporation. MD is a medical advisor for MT-1186-A02 study. DS, TF, AW, AS and SA are employees of Mitsubishi Tanabe Pharma America, Inc. VT is an employee of Mitsubishi Tanabe Pharma Europe Ltd. MH is an employee of Mitsubishi Tanabe Pharma Corporation.

### **Encore of 2023 ENCALS, 2023 Neuromuscular Study Group (NMSG) Annual Meeting**

#804 Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamic Effects of AOC 1020 Administered Intravenously to Adult Patients with Facioscapulohumeral Muscular Dystrophy (FORTITUDE™) Trial Design

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**Introduction:** FSHD is a rare, progressive, often asymmetric, genetic disease caused by aberrant expression of DUX4 in skeletal muscle, leading to a series of downstream events that result in degeneration and wasting. Strategies targeting DUX4 expression in skeletal muscle of individuals with FSHD via oligonucleotides are promising therapeutic approaches.

AOC 1020 is an antibody-oligonucleotide conjugate (AOC™) comprised of a humanized anti-transferrin receptor 1 (TfR1) antibody conjugated to a DUX4-targeting siRNA.

**Objective:** To evaluate the safety and tolerability of AOC 1020 in participants with FSHD.

**Methods:** This phase 1/2 study (NCT05747924) is a randomized, placebo-controlled, double-blind trial. The study will enroll 72 adults aged 18 to 65 years with a genetic diagnosis of FSHD1 or FSHD2. All participants will receive 5 doses of study medication administered quarterly with 1 booster at 6 weeks. Part A utilizes a dose-titration design to evaluate the safety of AOC 1020 at 2 low doses. Part B is a nested single/multiple-ascending dose design evaluating 2 higher doses. Staggered cohorts will be initiated based on a safety data review of the preceding cohorts. Part C is a parallel, placebo-controlled design to be conducted with 2 selected doses to evaluate exploratory clinical outcomes. After their final dose, participants enter a 3-month follow-up period. The total duration is 12 months. Eligible participants may enroll in an open-label extension study.

The primary objective of the study is to evaluate safety and tolerability. Secondary objectives include PK of AOC 1020. Exploratory measures of efficacy will be evaluated.

**Results/Conclusions:** N/A



## #805 Phase 1/2 Trial Evaluating AOC 1044 in Healthy Volunteers and Participants with DMD Mutations Amenable to Exon 44 Skipping (DMD44): EXPLORE44™ Trial Design

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**Introduction:** Duchenne muscular dystrophy (DMD) is a X-linked muscular disease caused by mutations in the DMD gene that prevent the expression of a functional dystrophin protein. Oligonucleotide-mediated skipping of DMD exons can restore the reading frame and dystrophin protein expression.

AOC 1044 is an antibody-oligonucleotide conjugate (AOC™) comprised of a humanized anti-transferrin receptor 1 (TfR1) antibody conjugated to phosphorodiamidate morpholino oligomers (PMOs).

**Objective:** To evaluate the safety and tolerability of single and multiple ascending doses of AOC 1044

**Methods:** EXPLORE44™ (NCT05670730) is a randomized, placebo-controlled, double-blind phase 1/2 trial conducted in two parts. Part A assesses the effects AOC 1044 in 5 single-dose cohorts of healthy volunteers, who are monitored for 3 months. Part B will assess the effects of AOC 1044 in 3 multiple-ascending dose-level cohorts of participants with DMD44, dosed no more frequently than once every 6 weeks for 3 months, with 3 months of follow-up.

The primary objective is safety and tolerability of single doses in healthy volunteers and multiple doses in participants with DMD44. Secondary objectives include pharmacokinetics and pharmacodynamics with exon 44 skipping (parts A and B) and dystrophin protein levels (part B). Exploratory objectives include measures of clinical activity, patient-reported outcomes, and quality of life in participants with DMD44.

Part A will enroll 40 healthy male volunteers (18-45 years). Part B will enroll 24 ambulatory or non-ambulatory males (7-27 years) with genetically confirmed DMD44. Eligible participants from part B will have the option to enroll in a planned open-label extension study.

**Sponsorship:** Avidity Biosciences, Inc

## #772 Longer Milestone-Free Time in IV Edaravone-Treated vs Non-IV Edaravone-Treated Patients With Amyotrophic Lateral Sclerosis: An Administrative Claims Analysis

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\*Former employee

**Introduction:** Intravenous (IV) edaravone was US Food and Drug Administration-approved for the treatment of amyotrophic lateral sclerosis (ALS) and was shown in clinical trials to slow the rate of physical functional decline.

**Objectives:** To estimate time to progression milestones in IV edaravone-treated vs IV edaravone-naïve patients with ALS in a real-world, retrospective observational analysis.

**Methods:** Patients with ALS who were continuously enrolled in Optum's de-identified Clinformatics® Data Mart between 8/8/2017–12/31/2021. IV edaravone-treated patients (cases) and non-IV edaravone-treated patients (controls) were propensity score-matched for the following covariates: age, race, geographic region, sex, insurance, riluzole prescription; and pre-index disease duration, cardiovascular disease, gastrostomy tube, artificial nutrition, noninvasive ventilation, and hospitalization. The index date was the first IV edaravone claim or when IV edaravone was available on the market, for cases or controls, respectively. Restricted mean time lost (RMTL) was calculated for the following milestones: use of canes/walkers/wheelchairs, artificial nutrition, noninvasive ventilation, invasive ventilation, speech-generating devices, and hospice.

**Results:** Cases (n=360) were matched to controls (n=360). For most reported milestones, cases had a longer milestone-free time than controls based on RMTL, except for speech-generating devices and invasive ventilation. More cases than controls reported no milestones and had fewer deaths from 0-12 months and 0-24 months, respectively, after the index date.

**Conclusions:** This analysis describes the time to milestones in IV edaravone-treated and IV edaravone-naïve patients with ALS in a real-world setting. This information may be useful to payers and clinicians in evaluating IV edaravone use.

**Sponsorship:** Mitsubishi Tanabe Pharma America, Inc.

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## #773 PGN-EDO51, an Enhanced Delivery Oligonucleotide (EDO) Candidate for the Treatment of Duchenne Muscular Dystrophy (DMD): Positive Results from a Phase 1 Study in Healthy Volunteers

Jane Larkindale, Pallavi Lonkar, Jaya Goyal, Ashling Holland, Jeffrey Foy, Brijesh Garg, Shaoxia Yu, Anthony Frank, Chris Abbott, Niels Svenstrup, Sarah Vacca, Michelle Mellion

(PepGen Inc., Boston, MA)

**Introduction:** PepGen's enhanced delivery oligonucleotide cell-penetrating peptide technology is engineered to optimize tissue delivery and cellular uptake of therapeutic oligonucleotides. PGN-EDO51 is being evaluated for the treatment of DMD amenable to exon 51 skipping.

**Objectives:** To evaluate the safety, tolerability, pharmacokinetics (plasma, urine, muscle), and pharmacodynamics (exon skipping) of single-ascending doses of PGN-EDO51 administered intravenously to healthy adult male volunteers (HV).

**Methods:** HVs were randomized (3:1 ratio) to receive a single dose of PGN-EDO51 or placebo. Biceps biopsies were performed.

**Results:** 32 HVs received PGN-EDO51 (1, 5, 10, or 15 mg/kg, n=6 per cohort) or placebo (n=8), and all completed the study. Majority of treatment-related adverse events were mild and resolved without intervention, including transient, reversible changes in kidney biomarkers (n=9) and hypomagnesemia (n=2) at the highest doses, with no significant clinical sequelae. On Day 28 following 15 mg/kg dose, dose-dependent and sustained concentrations of PGN-EDO51 up to 50 nM and dose-dependent increases in mean exon skipping of up to 2.0% (by ddPCR) were measured in biceps biopsies.

**Conclusions:** PGN-EDO51 demonstrated a generally tolerable profile at clinically relevant doses and exhibited high levels of muscle oligonucleotide delivery and exon 51 skipping. When compared to publicly available clinical data for other approaches, these are the highest levels measured in a clinical study after a single dose of oligonucleotide in HVs, supporting the hypothesis of enhanced delivery. Potential accumulation of exon 51 skipped transcripts and dystrophin protein with repeat dosing in people with DMD amenable to exon 51 skipping support the design of Phase 2 studies.

## #809 Preliminary Results from MLB-01-003: An Open Label Phase 2 Study of BBP-418 in Patients with Limb-girdle Muscular Dystrophy Type 2I

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**Introduction:** Limb-girdle Muscular Dystrophy (LGMD) Type 2I, also called LGMDR9 FKRP-related, is caused by bi-allelic partial loss-of-function of the fukutin-related protein (FKRP) gene, which results in hypoglycosylation of alpha-dystroglycan ( $\alpha$ DG). BBP-418 is an oral substrate supplementation therapy intended to saturate the partially functional FKRP enzyme, driving increased glycosylation of  $\alpha$ DG, and potentially ameliorating the root cause of LGMD2I.

**Objectives and Methods:** The ongoing Phase 2 is an open label dose escalation study investigating the safety and tolerability of BBP-418. Part 1 involved three dose cohorts (6 g QD, 6 g BID, 12 g BID BBP-418) treated for 3 months. During Part 2 and OLE (Part 3), all patients received 12 g BID of BBP-418, dose adjusted for weight.

**Results:** 14 patients with LGMD2I (aged 12-53, 8/14 homozygous for the L276I mutation) were enrolled. Participants showed increased levels of glycosylated  $\alpha$ DG after 90 days of dosing, median 33.4% of normal with BBP-418 compared to a baseline of 7.4%, which was sustained through 15 months. A sustained reduction in creatine kinase (CK) of >75% was observed through 15 months. Following 15 months of dosing with BBP-418, increased NSAD (+0.80 points) and 10MWT velocity (+0.12 m/s) and decreased 100MTT time (-2.82 seconds) were observed. BBP-418 was well-tolerated with no observed treatment-related serious adverse events, dose limiting toxicities or discontinuations. Updated data will be provided at the meeting.

**Conclusions:** Preliminary data from patients with LGMD2I suggest a positive effect of BBP-418 on levels of glycosylated  $\alpha$ DG, CK, NSAD, 100MTT, and 10MWT velocity. A global, double-blind placebo-controlled Phase 3 is ongoing.

## #818 Empasiprubart (ARGX-117) in Multifocal Motor Neuropathy: Interim Baseline Characteristics of the Phase 2 ARDA Study

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**Introduction:** Multifocal motor neuropathy (MMN) is a chronic, immune-mediated neuropathy characterized by progressive asymmetric weakness. MMN is often associated with anti-GM1 IgM autoimmunity, leading to activation of the classical complement pathway, driving subsequent axon damage. Empasiprubart (ARGX-117), an antibody that inhibits complement factor 2, was shown *in vitro* to block IgM-mediated classical pathway complement activation targeting motor neurons in MMN. This Phase 2, multicenter, randomized, placebo controlled, double-blinded, parallel-group study (ARDA, NCT05225675) will assess safety, efficacy, pharmacokinetics, pharmacodynamics, and immunogenicity of empasiprubart in adults with MMN.

**Objective:** To present baseline characteristics of the to date randomized patients

**Methods:** ARDA will recruit 48 participants with probable or definite MMN (per 2010 EFNS/PNS guidelines). All must have proven IVIg dependency and on a stable IVIg regimen. MMN diagnosis and IVIg dependency must be confirmed by a MMN confirmation committee. Enrolled participants will be assigned to one of two dosing cohorts (16 randomized to empasiprubart, 8 to placebo per cohort).

**Results:** As of 1 March 2023, 16 participants were randomized (7-USA, 9-Europe). Most (12) were classified as definite MMN. The median age was 55 (range 37-76) years, 68.8% were male. Pre-randomization IVIg intervals were every 2 weeks (5 patients), 3 weeks (4) and 4 weeks (7) with a median dose of 1.60 g/kg (range 1.25-1.97). Of the 16 randomized patients, 9 completed a formal IVIg dependency period and 7 were determined to be IVIg dependent and were allowed to bypass the dependency phase

**Conclusions:** This ongoing ARDA study will inform future complement-inhibition studies in patients with MMN.

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**LvdP** employer received fees for ad hoc consultancy from Argenx, Takeda, Biogen, Roche and Novartis gene therapies.

**SP** received lecture honoraria from argenx, Viatrix, Pfizer, Teva Actavis, Berlin Chemie Menarini, Mylan, Worwag, Adoc, Remedica and Salveo; research grants from argenx, Kedrion and Octapharma; consultant fees from argenx, Dianthus therapeutics and Mylan; and travel grants from Octapharma, Kedrion, Teva Actavis, Sanofi Genzyme, Pfizer, Roche, Adoc, Worwag, Medis, and Berlin Chemie Menarini; and reports no other conflicts of interest outside or related to this work.

**LQ** 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. Received speaker or expert testimony honoraria from CSL Behring, Novartis, Sanofi-Genzyme, Merck, Annexon, Alnylam, Biogen, Janssen, Lundbeck, ArgenX, UCB, LFB, Avilar Therapeutics, Octapharma and Roche. Serves at Clinical Trial Steering Committee for Sanofi Genzyme, and was Principal Investigator for UCB's CIDP01 trial.

**YH** reports no disclosures

**IVW, IVH, EP, SBS** are employees of argenx

**OVS** works as a consultant for argenx.

**MV, PD** works as a consultant for argenx and PPD.

**JA** has received consulting honoraria from argenx, Alexion, Akcea, CSL Behring, Johnson & Johnson, Grifols, Takeda, and Sanofi.

Marc: 413-265-1121

#825- DESIGN OF A PHASE 2, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY OF NIPOCALIMAB IN PARTICIPANTS WITH ACTIVE IDIOPATHIC INFLAMMATORY MYOPATHIES (SPIREA)

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\*Presenting author.

**Introduction:** Idiopathic inflammatory myopathies (IIM) are a rare group of systemic autoimmune diseases characterized by progressive muscular weakness and internal organ involvement, often leading to physical disability and decreased quality of life. Nipocalimab is designed to address the underlying disease pathology by selectively blocking the neonatal Fc receptor to reduce pathogenic autoantibodies. In a phase 2 study of generalized myasthenia gravis (NCT03772587), nipocalimab lowered pathogenic IgG autoantibody levels with significant clinical benefit, acceptable safety, and a favorable benefit-risk profile.

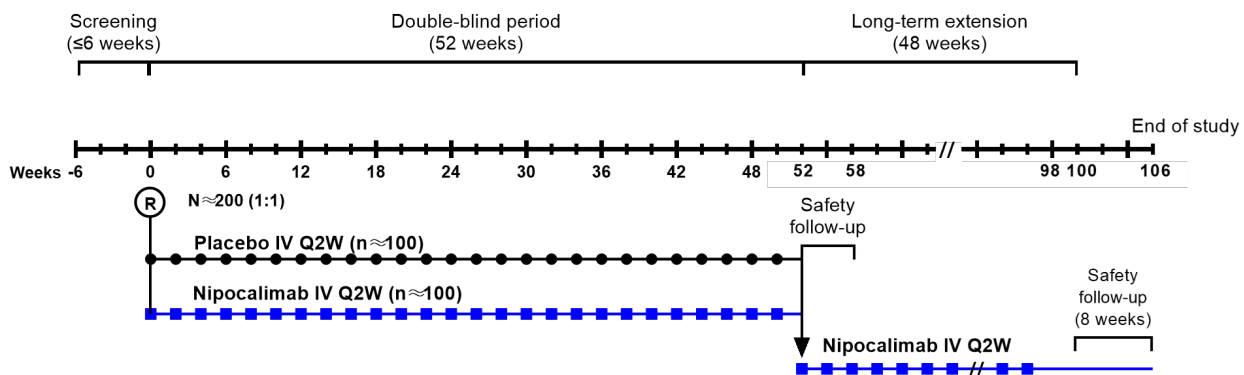
**Objective:** To describe the study design of SPIREA (NCT05379634) which aims to evaluate the efficacy and safety of nipocalimab in patients with IIM.

**Methods:** SPIREA is a phase 2, double-blind, placebo-controlled, randomized clinical trial enrolling adults (N≈200) with active IIM. The study comprises screening, double-blind treatment, long-term extension, and follow-up periods (**Figure 1**). Randomized participants are treated every 2 weeks with intravenous nipocalimab or placebo through Week 50. Background oral glucocorticoid (GC) doses will be tapered from Weeks 24–44.

**Results:** The primary endpoint is the proportion of participants who achieve at least minimal improvement (≥20) in American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Total Improvement Score (TIS) at Week 52 and on ≤5 mg/day of oral GC from Weeks 44–52. Secondary endpoints include the proportion of participants who achieve ≥20-point improvement in TIS at Weeks 24 and 52.

**Conclusions:** The ongoing SPIREA study evaluating nipocalimab’s safety and efficacy in patients with IIM will help to validate the ACR/EULAR-TIS endpoint in IIM and the role of nipocalimab as a steroid sparing agent in IIM.

Figure 1. Study Design.



IV, intravenous; Q2W, every 2 weeks; R, randomization.



#737 Design of REACH: Phase 3 Randomized, Double-Blind, Placebo-Controlled, 48-Week Study of the Efficacy and Safety of Losmapimod in FSHD

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FSHD is a chronic, variably progressive disease leading to accumulation of disability over decades. Nonclinical studies have shown that losmapimod (a small molecule p38  $\alpha/\beta$  MAPK inhibitor) reduces the aberrant expression of DUX4, the underlying cause of FSHD. Two Phase 2 clinical studies, a 48-week randomized controlled study (ReDUX4, FIS-002-2019) and a 52-week open-label study (OLS, FIS-001-2019) demonstrated evidence of benefit of treatment with losmapimod on muscle structure and function, as well as FSHD-relevant clinical endpoints that are recognized by patients and favorable safety and tolerability, supporting continued development. Fulcrum has initiated a Phase 3 double-blind, placebo-controlled trial to support the development of losmapimod in FSHD. Approximately 230 people with FSHD, 210 with genetically confirmed FSHD1 and 20 with FSHD2, will be randomized 1:1 to receive losmapimod or placebo orally, twice daily for 48-weeks. The primary endpoint is reachable workspace quantification of total relative surface area (Q1-Q5) with 500 g wrist weight in the dominant arm, with secondary efficacy endpoints of quality of life in the neurological disorders upper extremity scale (Neuro-QoL UE), patient global impression of change (PGIC), and muscle fat infiltration (MFI) using whole-body musculoskeletal MRI (WB-MSK MRI). Exploratory assessments include muscle fat fraction, muscle strength by hand-held dynamometry, and patient reported outcomes (PROs) including patient global impression of severity (PGIS), a novel FSHD PRO, numeric pain rating scale (NPRS), 5-level EQ-5D (EQ-5D-5L) and healthcare utilization questionnaire. The design of this Phase 3 study will be presented.



#738 Safety and Tolerability of Losmapimod for the Treatment of FSHD

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FSHD is a variably progressive disease leading to accumulation of disability over decades. Fulcrum has assessed losmapimod, a small-molecule p38  $\alpha/\beta$  MAPK inhibitor, in FSHD in one completed Phase 1 study (FIS-001-2018) and two ongoing Phase 2 studies (FIS-001-2019, FIS-002-2019) in the open-label extension period. Subjects aged 18-65 years with genetically confirmed FSHD1, Clinical Severity Score 2-4, and MRI-eligible muscles for biopsy were exposed to losmapimod 7.5 or 15 mg BID PO for 14 days and up to 96 weeks. In Study FIS 001-2018, 6 subjects were exposed to 7.5 mg and 11 subjects to 15 mg BID dosing for 14 consecutive days. In Studies FIS-001-2019 and FIS-002-2019, 14 and 77 subjects respectively, received at least one dose of losmapimod 15 mg BID for up to 96 weeks. A total of 108 subjects with FSHD1 have been exposed to losmapimod. Most AEs observed during the studies were considered mild to moderate in severity. Most common AEs were eczema, dry skin, ALT increase, rash, headache, and myalgia. Most AEs resolved with continued dosing. Dosing was paused for 14 days in four subjects (3 in FIS 001-2019, 1 in FIS-002-2019) due to COVID-19 infection. No drug-related SAEs, deaths, discontinuations due to AEs, or clinically significant changes in vital signs, clinical laboratory results, or ECG parameters were reported. Losmapimod administered up to 15 mg BID in >100 subjects with FSHD1 for up to 96 weeks has been generally well-tolerated; the benefit-risk profile of losmapimod for treatment of FSHD remains positive and favorable.

#734 A Phase 1/2a, Randomized, Double-Blind, Placebo-Controlled, First-in-patient Study of JM17 To Evaluate safety, Tolerability, Pharmacokinetics, and Pharmacodynamics in Adults with Spinal and Bulbar Muscular Atrophy

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**Introduction:** Spinal and Bulbar Muscular Atrophy (SBMA) is a rare, X-linked lower motor neuron disease with an abnormal expansion of CAG repeat in the androgen receptor (AR) gene. JM17 is a novel Nrf2 activator that was shown to reduce accumulation of mutant polyQ AR protein in muscles and to improve motor functions in SBMA mouse model. Previous Phase I study in healthy volunteers has demonstrated a favorable safety and drug-like profile of JM17 (NCT04392830).

**Objectives:** This study aims to further characterize the safety, tolerability, pharmacokinetics, pharmacodynamics of JM17 in adult male SBMA patients (NCT05517603).

**Methods:** This is an international multicenter study. Approximately 24 subjects with SBMA aged  $\geq 18$  years will be randomized in 3:1 ratio to receive either 600 mg of JM17 or placebo once daily in oral suspension for 12 weeks. A safety follow-up visit will be scheduled 4 weeks after the end of treatment. The primary objectives are the safety of JM17. The secondary objectives are the pharmacokinetics and the pharmacodynamics of JM17 as evaluated by the level of mutant AR protein and the transcriptome in skeletal muscles. Exploratory objectives included clinical assessments in muscle strength, volume, and function as well as patient reported outcomes.

**Results:** Topline data are expected to be available in 2024.

**Conclusions:** This is the first-in-patient proof-of-mechanism study to demonstrate the therapeutic potential of JM17 in SBMA. The results from the Phase I study and this study will provide important information to optimize dose selection in the next efficacy study.

## #806 Rozanolixizumab in Muscle-specific Kinase Autoantibody-positive Myasthenia Gravis: Further Analyses from MycarinG Study

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(Nice, France; \*Orange, CA; \*\*Rome, Italy; \*\*\*Barcelona, Spain; \*\*\*\*Lübeck, Germany; \*\*\*\*\*Lexington, KY; \*\*\*\*\*Milan, Italy; \*\*\*\*\*Indianapolis, IN; \*\*\*\*\*Hanamaki, Japan; \*\*\*\*\*Copenhagen, Denmark; \*\*\*\*\*Tampa, FL; \*\*\*\*\*Münster, Germany; \*\*\*\*\*Monheim, Germany; \*\*\*\*\*Madrid, Spain; \*\*\*\*\*Slough, UK; \*\*\*\*\*Toronto, Canada)

**Introduction:** Muscle-specific kinase autoantibody-positive (MuSK-Ab+) generalized myasthenia gravis (gMG) is usually more clinically severe than acetylcholine receptor autoantibody-positive (AChR-Ab+) gMG.

**Objectives:** To evaluate clinical outcomes of rozanolixizumab in MuSK-Ab+ gMG using data from the Phase 3 MycarinG study.

**Methods:** MycarinG (MG0003/NCT03971422) randomized adults with Myasthenia Gravis Foundation of America Class II–IVa, AChR-Ab+ or MuSK-Ab+ gMG to weekly rozanolixizumab 7mg/kg, 10mg/kg or placebo for 6 weeks. The primary endpoint was Day 43 change from baseline (CFB) in Myasthenia Gravis Activities of Daily Living (MG-ADL).

**Results:** 200 patients (21 MuSK-Ab+) were randomized to rozanolixizumab 7mg/kg (n=66 [5 MuSK-Ab+]), 10mg/kg (n=67 [8]) or placebo (n=67 [8]). Among patients with MuSK-Ab+ gMG, a higher proportion experienced prior MG crisis and a lower proportion had thymectomy than the overall population, and baseline MG-ADL score was higher (Table 1). Day 43 least-squares mean CFB in MG-ADL for 7mg/kg, 10mg/kg and placebo groups were -7.28, -4.16 and 2.28, respectively, in patients with MuSK-Ab+ gMG and -3.37, -3.40 and -0.78 in the overall population (Figure 1). Mean percentage CFB in total immunoglobulin G (IgG) and IgG4 for patients with MuSK-Ab+ gMG and the overall population are presented in Table 2. Treatment-emergent adverse events occurred in 81.3% (7mg/kg), 82.6% (10mg/kg) and 67.2% (placebo) patients in the overall population and most were mild-to-moderate in severity.

**Conclusion:** Rozanolixizumab lowered total and subclass IgG levels and improved MG-specific outcomes in MuSK-Ab+ gMG, consistent with the overall study population. Funding: UCB Pharma.

**Table 1: Baseline characteristics of patients with MuSK-Ab+ gMG and in the overall population**

	MuSK-Ab+*			Overall population <sup>†</sup>			
	Placebo (n=8)	RLZ 7mg/kg (n=5)	RLZ 10mg/kg (n=8)	Placebo (n=67)	RLZ 7mg/kg (n=66)	RLZ 10mg/kg (n=67)	
Age at initial diagnosis, years, mean (SD)	37.1 (10.0)	37.2 (13.7)	43.6 (16.9)	41.4 (19.1)	46.6 (16.0)	42.6 (19.1)	
Race, n (%)	Asian	0	2 (40.0)	2 (25.0)	5 (7.5)	7 (10.4)	
	Black	0	0	1 (12.5)	1 (1.5)	4 (6.0)	
	Native Hawaiian or other Pacific Islander	0	0	0	1 (1.5)	0	
	White	8 (100)	3 (60.0)	5 (62.5)	46 (68.7)	41 (62.1)	49 (73.1)
	Missing <sup>‡</sup>	0	0	0	14 (20.9)	16 (24.2)	7 (10.4)
Duration of disease, years, mean (SD)	10.2 (9.8)	13.9 (7.6)	5.2 (5.0)	9.4 (9.3)	6.9 (6.8)	9.6 (9.9)	
MG-ADL score at baseline, mean (SD)	8.8 (3.7)	11.0 (3.5)	9.3 (2.7)	8.4 (3.4)	8.4 (3.8)	8.1 (2.9)	
QMG score at baseline, mean (SD)	17.9 (4.0)	17.0 (5.8)	14.0 (3.6)	15.8 (3.5)	15.4 (3.7)	15.6 (3.7)	
MGFA disease class at baseline, n (%)	Class II	1 (12.5)	3 (60.0)	3 (37.5)	23 (34.3)	29 (43.9)	26 (38.8)
	Class III	4 (50.0)	2 (40.0)	5 (62.5)	41 (61.2)	34 (51.5)	39 (58.2)
	Class IVa/b <sup>‡</sup>	3 (37.5)	0	0	3 (4.5)	3 (4.5)	2 (3.0)
Prior MG crisis, n (%)	5 (62.5)	3 (60.0)	4 (50.0)	23 (34.3)	19 (28.8)	17 (25.4)	
Baseline medications, n (%)	1 baseline MG-specific therapy (excluding AChEI)	1 (12.5)	1 (20.0)	4 (50.0)	23 (34.3)	19 (28.8)	26 (38.8)
	≥2 baseline MG-specific therapies (excluding AChEI)	4 (50.0)	3 (60.0)	4 (50.0)	27 (40.3)	30 (45.5)	34 (50.7)
	Thymectomy at baseline, n (%)	3 (37.5)	1 (20.0)	0	31 (46.3)	32 (48.5)	20 (29.9)
Total IgG, g/L, mean (SD)	9.5 (3.0)	9.2 (1.0)	9.3 (2.2)	10.2 (2.6)	10.2 (3.2)	9.7 (2.6)	

\*Includes two patients who had positive AChR and MuSK autoantibody status.

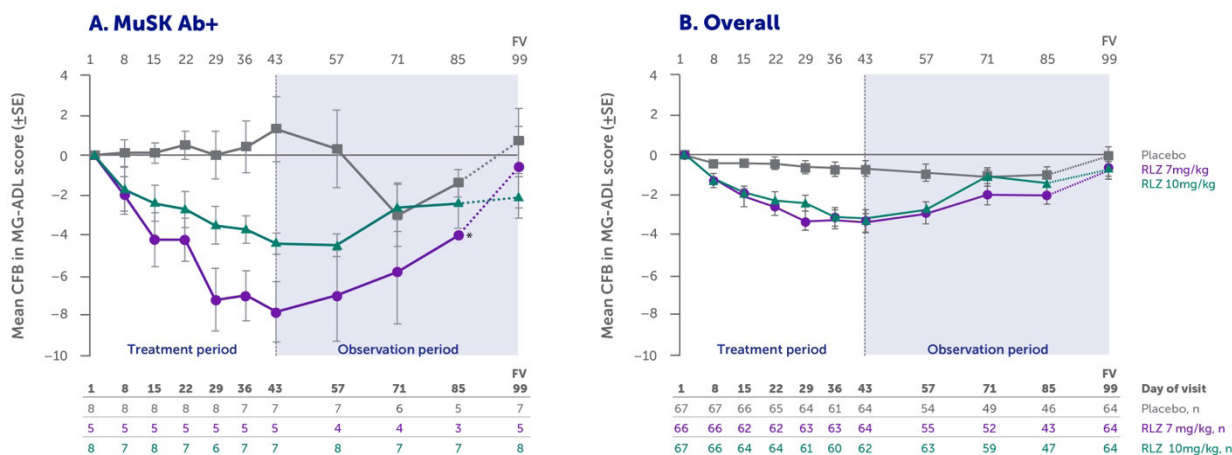
<sup>†</sup>Includes both patients with AChR-Ab+ and MuSK-Ab+ gMG.

<sup>‡</sup>Data on race were not permitted to be collected in certain countries.

<sup>§</sup>Only 1 patient, who was randomised to the placebo group, had Class IVb disease.

AChEI, acetylcholinesterase inhibitor; AChR-Ab+, acetylcholine receptor autoantibody-positive; gMG, generalised myasthenia gravis; IgG, immunoglobulin G; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; MuSK-Ab+, muscle-specific kinase autoantibody-positive; QMG, quantitative myasthenia gravis; RLZ, rozanolizumab; SD, standard deviation.

**Fig 1: Mean change from baseline in MG-ADL in (A) patients with MuSK-Ab+ gMG and (B) the overall population**



\*SD was not calculated for populations with n less than 3.

FV, final visit; gMG, generalised myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MuSK Ab+, muscle-specific kinase autoantibody-positive; RLZ, rozanolizumab; SE, standard error.

**Table 2: Mean percentage change from baseline in total IgG and IgG4 for patients with MuSK-Ab+ gMG and in the overall population**

	MuSK-Ab+*			Overall population <sup>†</sup>		
	Placebo (n=8)	RLZ 7mg/kg (n=5)	RLZ 10mg/kg (n=8)	Placebo (n=67)	RLZ 7mg/kg (n=66)	RLZ 10mg/kg (n=67)
Total IgG (%)	-1.3	-75.9	-77.6	-4.2	-69.1	-71.4
IgG4 (%)	10.14	-69.47	-66.95	-5.29	-56.57	-59.87

\*Includes two patients who had positive AChR and MuSK autoantibody status.

<sup>†</sup>Includes both patients with AChR-Ab+ and MuSK-Ab+ gMG.

AChR, acetylcholine receptor; gMG, generalised myasthenia gravis; IgG, immunoglobulin G; MuSK-Ab+, muscle-specific kinase autoantibody-positive; RLZ, rozanolizumab.

## #751 Ataluren preserves muscle function in nmDMD patients: a pooled analysis of results from three randomized, double-blind, placebo-controlled trials

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**Introduction:** Study 041 (NCT03179631) is a phase 3, randomized, placebo-controlled 72-week ataluren trial in nonsense mutation Duchenne muscular dystrophy (nmDMD) patients.

**Objectives:** To describe results of a pooled analysis of ataluren muscle function efficacy results from Study 041 and two randomized, placebo-controlled 48-week ataluren trials (Study 007 [phase 2b] and Study 020 [phase 3]).

**Methods:** Patients were eligible if they were male, had phenotypic evidence of DMD, and had an nmDMD diagnosis confirmed by genetic testing. Patients were randomized 1:1 (ataluren:placebo). Pooled efficacy results for 48-week change in 6-minute walk distance (6MWD), North Star Ambulatory Assessment (NSAA) total and linear scores (where available), and timed function tests (TFTs; 10m walk/run, 4-stair ascent and 4-stair descent) are described for the overall pooled study population; and 48-week change in 6MWD for a key subgroup with baseline 6MWD 300–400m.

**Results:** The pooled study population included 354 patients receiving ataluren and 347 patients receiving placebo. Treatment with ataluren significantly reduced mean change from baseline in all measures vs placebo for the overall population (6MWD: 19.3m,  $p=0.0002$ ; NSAA total score: 1.07,  $p=0.0010$ ; NSAA linear score: 2.70,  $p=0.0031$ ; 10m walk/run time: -1.31s,  $p=0.0001$ ; 4-stair ascent time: -1.45s ( $p=0.0003$ ); 4-stair descent time: -1.54s,  $p=0.0003$ ). The pooled subgroup with baseline 6MWD 300–400m included 155 patients receiving ataluren and 157 patients receiving placebo. Ataluren preserved 32.1m of 6MWD in this subgroup vs placebo ( $p=0.0005$ )

**Conclusions:** Pooled placebo-controlled clinical trial data from 701 patients demonstrate that ataluren preserves muscle function, assessed by clinical meaningful endpoints, in nmDMD patients.

#739 Therapeutic Play Gym: A caregiver-mediated exercise system for infants and young children with severe neuromuscular weakness- Feasibility and Extension Study

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**Introduction:** Children need stability, self-produced sensorimotor experiences, and variable practice to master developmental skills in supine, side-lying, prone, and supported seated positions.

**Objective:** To evaluate the effect, safety, and the feasibility of caregiver-mediated exercise training using a novel Therapeutic Play Gym (TPG).

**Methods:** Nine children ages 4-58 months (ventilation dependence=9, G-tube dependence=6) with diagnoses of Spinal Muscular Atrophy (SMA) Type 0, SMA Type 1, X-Linked Myotubular Myopathy, and Nemaline Rod Muscular Dystrophy and their caregivers enrolled in the study. Dyads completed baseline (BL), Month 3, and Month 6 end of study (EOS) testing with the exploratory TPG-specific FUNctional Measure (FUNM), Neuromuscular Gross Motor Outcome (GRO), and Caregiver Impression of Change Questionnaire (CICQ). Testing was performed in the home environment or during naturally occurring episodes of care at The University of Florida.

**Study results:** Participants logged 28,642 training minutes with no TPG-related adverse events (AEs). All outcomes captured a statistically significant change in function: BL FUNM (not in TPG) to EOS FUNM (in TPG)  $p=0.013$ , No TPG at BL to EOS  $p=.0087$ , Neuro GRO BL to EOS  $p=.0264$ , CGIC  $p<.0001$ .

**Conclusion:** Exercise training using the TPG device is yielding promising in functional ability and caregiver reported quality of life. 8 dyads are enrolled in a 2-year extension study.

## #732 Endosomal Escape Vehicle (EEV™) - Oligonucleotide Conjugates Produce Exon Skipping and Dystrophin Production in Preclinical Models of Duchenne Muscular Dystrophy

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**Introduction:** Antisense phosphorodiamidate morpholino oligomer (PMO)-mediated exon skipping therapies for Duchenne muscular dystrophy (DMD) produce only a very modest amount of dystrophin in skeletal and cardiac muscle. To enhance PMO delivery to target tissues, we designed a family of proprietary cyclic cell-penetrating peptides that form the core of the Endosomal Escape Vehicle (EEV™) platform.

**Objective:** Assess the therapeutic potential of EEV-PMO conjugates for exon 44 and 45 skip amenable DMD in preclinical models.

**Methods:** Efficacy of EEV-PMO conjugates were assessed in several cell and animal models. EEV-PMO-23 (EEV-exon 23 skipping PMO conjugate) was administered to D2-*mdx* mice intravenously (IV). Efficacy of ENTR-601-44 (EEV-exon 44 skipping PMO conjugate) and ENTR-601-45 (EEV-exon 45 skipping PMO conjugate) were also assessed in several cell and animal models.

**Results:** D2-*mdx* mice administered EEV-PMO-23 demonstrated robust exon skipping and dystrophin production in both skeletal and cardiac muscle and improved skeletal muscle contractile force to wild type levels. Next, efficacy of exon 44 and 45 skip amenable EEV-PMO conjugates were assessed. ENTR-601-44 showed durable exon skipping in skeletal and cardiac muscle in non-human primates for at least 12 weeks following a single IV dose. Additionally, ENTR-601-45 produced robust exon skipping and dystrophin production in skeletal and cardiac muscle cells derived from patients with exon 45 skip amenable DMD.

**Conclusions:** These results demonstrate the ability of the EEV platform to efficiently deliver exon skipping oligonucleotides to skeletal and cardiac muscle in preclinical models of DMD and support the potential for further study in patients with DMD amenable to exon 44 and 45 skipping.



## #842 Matching-adjusted indirect comparison of ravulizumab/efgartigimod in generalized myasthenia gravis: Timepoint challenges

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**Introduction:** Matching-adjusted indirect comparisons (MAICs) may be used to assess the benefits of different treatments for symptom control. In this MAIC, we built on findings from previous comparisons of ravulizumab and efgartigimod and used mean changes from baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) scores from the CHAMPION-MG and ADAPT trials to assess the effects of these treatments on symptom control in patients with gMG at different timepoints.

**Methods:** Individual patient-level data from CHAMPION-MG were weighted to match summary baseline characteristics from the acetylcholine receptor antibody-positivesubset of patients in ADAPT at the trial-arm level, and mean changes in MG-ADL scores from baseline to different timepoints were compared. Anchored comparisons were performed at Weeks 4 and 10, and at Week 8 (efgartigimod) vs Week 26 (ravulizumab).

**Results:** Baseline characteristics of the patients before and after matching are shown in Table 1. The timepoints chosen to assess the impact of ravulizumab and efgartigimod on MG-ADL were found to affect the results. Improvements in MG-ADL scores appeared to favour efgartigimod vs ravulizumab at Week 4, whereas at Week 10, and Week 8 (efgartigimod) vs Week 26 (ravulizumab), the results trended in favour of ravulizumab (Table 2).

**Conclusion:** Outcomes of indirect comparisons of the effects of efgartigimod and ravulizumab on symptom control in patients with gMG can vary depending on the chosen timepoints and matching methodology. The consistency of symptom control achievable over a prolonged period should be considered, alongside efficacy and tolerability, when assessing treatment options for patients with gMG.

### Disclosures:

S. Meuth: Received speaker fees and advisory honoraria from Almirall, Amicus Therapeutics Germany, Bayer Health Care, Biogen, Celgene, Diamed, Genzyme, MedDay Pharmaceuticals, Merck Healthcare, Novartis, Novo Nordisk, ONO Pharma, Roche, Sanofi-Aventis, Chugai Pharma, QuintilesIMS and Teva; research funding from the German Ministry for Education and Research, Deutschen Forschungsgesellschaft, Else Kröner Fresenius Foundation, German Academic Exchange Service, Hertie Foundation, Interdisciplinary Center for Clinical Studies Muenster, German Foundation Neurology and by Almirall, Amicus Therapeutics Germany, Biogen Idec, Diamed, Fresenius Medical Care, Genzyme, Merck Healthcare, Novartis, ONO Pharma, Roche, and Teva  
T. Hagenacker: Received speaker fees and advisory honoraria from Alexion, Hormosan, Roche, Biogen and Argenx  
C. Scheiner: Consultant for Alexion and CSL Behring GmbH  
M. Masuda:  
A. Kielhorn: Employee of Alexion  
B. Werneburg: Employee of Alexion at the time of the study  
L. Powell: Employee of Broadstreet HEOR which received funding from Alexion to conduct this work  
B. Rogula: Employee of Broadstreet HEOR which received funding from Alexion to conduct this work  
K. Johnston: Employee of Broadstreet HEOR which received funding from Alexion to conduct this work



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**Tables:**

**Table 1. Baseline characteristics before and after matching**

	CHAMPION						ADAPT (AChR-Ab+ patients)		
	Ravulizumab (n=86)		Placebo (n=89)		Total (n=175)		Efgartigimod (n=65)	Placebo (n=64)	Total (n=129)
	Unmatched	Matched	Unmatched	Matched	Unmatched	Matched			
Mean age, years	58.0	44.7	53.3	49.2	55.6	47.0	44.7	49.2	46.9
Female, n (%)	44 (51.2)	61 (70.8)	45 (50.6)	56 (62.5)	89 (50.9)	116 (66.6)	46 (70.8)	40 (62.5)	86 (66.7)
MGFA class II, n (%)	39 (45.3)	37 (43.1)	39 (43.8)	35 (39.1)	78 (44.6)	72 (41.0)	28 (43.1)	25 (39.1)	53 (41.1)
MGFA class III, n (%)	41 (47.7)	46 (53.8)	45 (50.6)	50 (56.3)	86 (49.1)	96 (55.1)	35 (53.8)	36 (56.3)	71 (55.0)
MGFA class IV, n (%)	6 (7.0)	3 (3.1)	5 (5.6)	4 (4.7)	11 (6.3)	7 (3.9)	2 (3.1)	3 (4.7)	5 (3.9)
Mean years since diagnosis	9.8	9.7	10.0	8.9	9.9	9.3	9.7	8.9	9.3
Mean MG-ADL score	9.1	9.0	8.9	8.6	9.0	8.8	9.0	8.6	8.8
Steroid use at study entry, n (%)	56 (65.1)	61 (70.8)	65 (73.0)	71 (79.7)	121 (69.1)	132 (75.3)	46 (70.8)	51 (79.7)	97 (75.2)
NSIST use at study entry, n (%)	56 (65.1)	53 (61.5)	63 (70.8)	51 (57.8)	119 (68.0)	104 (59.6)	40 (61.5)	37 (57.8)	77 (59.7)

AChR-Ab+, acetylcholine receptor antibody-positive; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGFA, Myasthenia Gravis Foundation of America; NSIST, non-steroidal immunosuppressant therapy.

**Table 2. Mean (95% confidence interval) MG-ADL changes from baseline to different timepoints**

Timepoint	Efgartigimod–placebo	Ravulizumab–placebo	Efgartigimod–ravulizumab
At Week 4	-2.8 (-3.8, -1.8)	-1.1 (-2.0, 0.3)	-1.6 (-3.0, -0.3)
At Week 10	-0.6 (-1.9, 0.6)	-1.6 (-2.6, -0.7)	1.0 (-0.5, 2.5)
At Week 8 (efgartigimod) vs Week 26 (ravulizumab)	-0.5 (-1.5, 0.6)	-1.7 (-2.7, -0.7)	1.2 (-0.2, 2.7)

MG-ADL, Myasthenia Gravis Activities of Daily Living.

## #843 Assessing the extent of symptom control provided by ravulizumab or efgartigimod to patients with generalized myasthenia gravis (gMG)

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**Introduction:** The levels of gMG symptom control achievable with ravulizumab and efgartigimod have been shown with Myasthenia Gravis Activities of Daily Living (MGADL) scores in the CHAMPION-MG and ADAPT trials, respectively.<sup>1,2</sup> This analysis used 10-week trajectories post-baseline in MG-ADL total scores to estimate the time patients spent in different health states with each treatment over 12 months.

**Methods:** Mean changes from baseline in MG-ADL over 26 weeks with ravulizumab and over 10 weeks with efgartigimod were extracted from the CHAMPION-MG and ADAPT, respectively. Changes were categorized into different health states: improvements or deteriorations ( $\geq 0.5$ -point difference) or steady ( $< 0.5$ -point difference) vs the previous observation (Figure 1). These observations were extrapolated to estimate trends over 12 months.

**Results:** Of 9 mean MG-ADL changes observed in patients on efgartigimod, 2 were improvements, 4 were steady (with statistically significant difference vs placebo;  $p < 0.0001$ ) and 3 were deteriorations vs the previous observations. Of 7 observations in patients on ravulizumab, 3 were improvements and 4 were steady (including 3 with statistically significant difference vs placebo;  $p < 0.0030$ ) vs the previous observations (Figure 2). After extrapolation, patients on ravulizumab were estimated to spend most (87.9%) of their time in the steady state, while those on efgartigimod were more widely distributed across health states (Figure 3).

**Conclusion:** Levels of symptom control were more widely distributed in patients treated with efgartigimod than ravulizumab. This should be considered with other factors, such as the burden of treatment administration, when selecting therapies for patients with gMG.

### Disclosures:

T. Hagenacker: Received speaker's fees as well as advisory honoraria from Alexion, Hormosan, Roche, Biogen and Argenc

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C. Scheiner: Consultant for Alexion and CSL Behring GmbH

M. Masuda:

A. Kielhorn: Employee of Alexion

B. Werneburg: Employee of Alexion at the time of the study

L. Powell: Employee of Broadstreet HEOR which received funding from Alexion to conduct this work

P. Jayasinghe: Employee of Broadstreet HEOR which received funding from Alexion to conduct this work

K. Johnston: Employee of Broadstreet HEOR which received funding from Alexion to conduct this work

**References:**

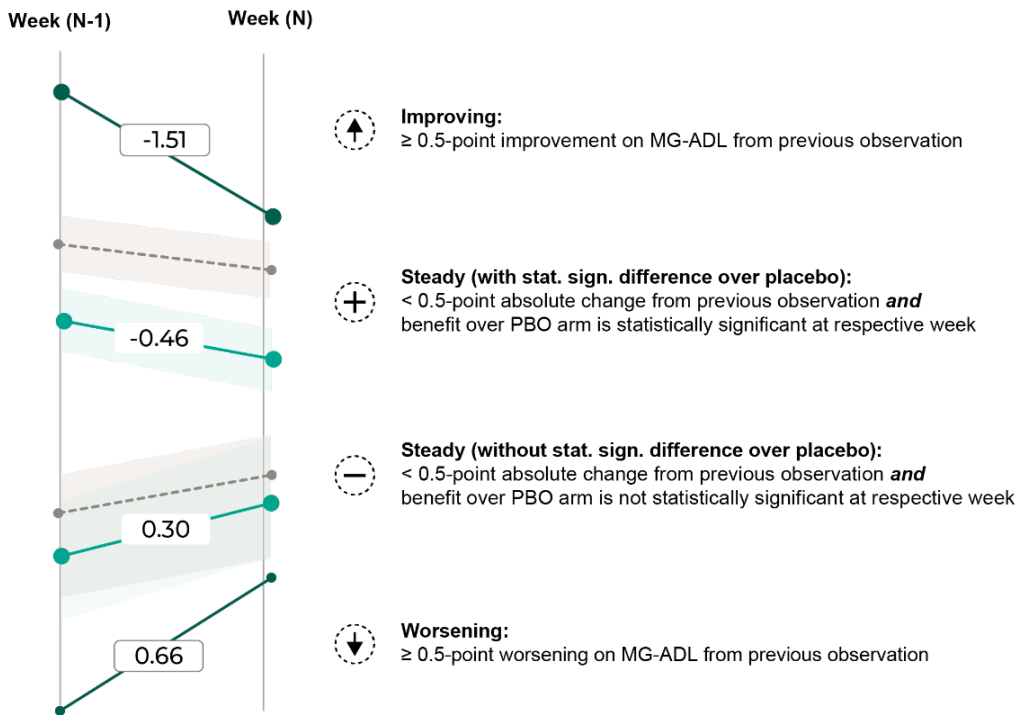
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The study was sponsored by Alexion Pharmaceuticals Inc., with medical writing support provided by Hannah Wedge of OPEN Health Communications.

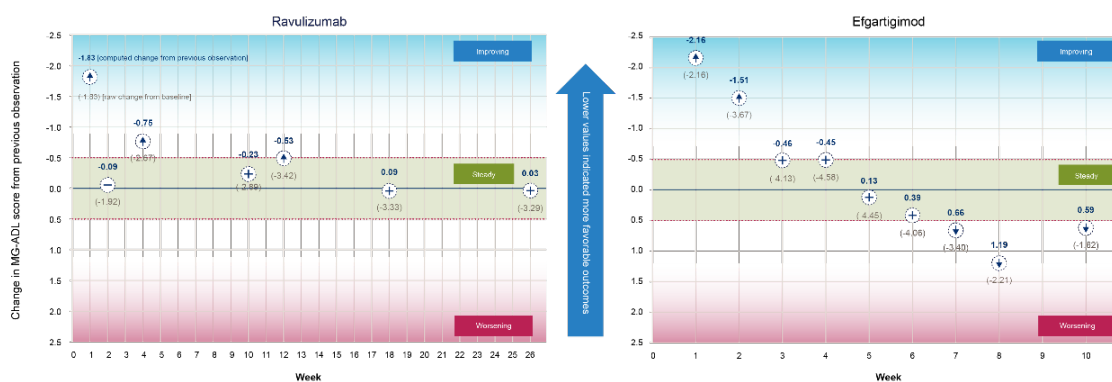
**Figures:**

**Figure 1. Definitions of the different health states**



MG-ADL, Myasthenia Gravis Activities of Daily Living; PBO, placebo.

Figure 2. Health states according to change in mean MG-ADL score from the previous observation for patients treated with ravulizumab or efgartigimod



- State:
- ▲ Improving:  $\geq 0.5$ -point improvement on MG-ADL from previous observation
  - ⊕ Steady (with stat. sign. difference over placebo):  $< 0.5$ -point absolute change from previous observation and benefit over PBO arm is statistically significant at respective week
  - ⊖ Steady (without stat. sign. difference over placebo):  $< 0.5$  point absolute change from previous observation and benefit over PBO arm is not statistically significant at respective week
  - ▼ Worsening:  $> 0.5$  point worsening on MG-ADL from previous observation

Grey values in parentheses show raw change from baseline; values in blue show the calculated change from the previous observation. MG-ADL, Myasthenia Gravis Activities of Daily Living.

All silicoptan doses (N=200)	
Any TEAE, n (%)	188 (94.0)
Serious TEAE, n (%)	64 (32.0)
TEAE resulting in permanent withdrawal from INP, n (%)	17 (8.5)
Treatment-related TEAE, n (%)	67 (33.5)
Severe TEAE, n (%)	57 (28.5)
TEAEs leading to death, n (%)	4 (2.0)

## #808 Long-term safety, efficacy & self-injection satisfaction with zilucoplan in myasthenia gravis: RAISE-XT interim analysis

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Oxford, UK; \*Nice, France; \*\*Columbus, OH; \*\*\*Montreal, Canada; \*\*\*\*Sheffield, UK; \*\*\*\*\*Austin, TX; \*\*\*\*\*Oslo, Norway; \*\*\*\*\*PV, Italy; \*\*\*\*\*Katowice, Poland; \*\*\*\*\*Hanamaki, Japan; \*\*\*\*\*Tampa, FL; \*\*\*\*\*Cambridge, MA; \*\*\*\*\*Monheim, Germany; \*\*\*\*\*Braine-l'Alleud, Belgium; \*\*\*\*\*Brussels, Belgium; \*\*\*\*\*Chapel Hill, NC

**Introduction:** Long-term data from RAISE-XT (NCT04225871), a Phase 3, multicenter, open-label extension study, will evaluate zilucoplan, a C5 complement inhibitor, in patients with generalized myasthenia gravis (gMG).

**Objectives:** To evaluate the long-term safety, efficacy, and self-injection satisfaction of zilucoplan in gMG.

**Methods:** Adults (aged 18–75 years) with gMG who completed a qualifying zilucoplan study (NCT03315130/NCT04115293 [RAISE]) self-administered daily subcutaneous injections of zilucoplan 0.3 mg/kg. Primary outcome was incidence of treatment-emergent adverse events (TEAEs). Secondary efficacy outcomes included change from qualifying study double-blind baseline in Myasthenia Gravis Activities of Daily Living (MG-ADL) score. The Self-Injection Assessment Questionnaire (SIAQ; scores 0–10; higher scores indicate more positive experience) was completed by US patients directly after self-injection and measured patient satisfaction with self-injection.

**Results:** At data cut-off (September 8, 2022), 200 patients had enrolled in RAISE-XT. Median (range) exposure was 1.2 (0.11–4.45) years. TEAEs occurred in 188 (94.0%) patients; 64 (32.0%) patients experienced a serious TEAE (Table). Mean (standard deviation) changes from double-blind baseline MG-ADL score continued to decrease through Extension Week 12 and were maintained through to Extension Week 48 (Week E48) for the zilucoplan and placebo-switch groups: –5.95 (4.14) and –6.85 (5.13) at Week E48, respectively (Figure 1). In the SIAQ domain of satisfaction with self-injection, median score was 8.20 (range: 3.9–10.0; n=63; Figure 2).

**Conclusions:** In this interim analysis of RAISE-XT, zilucoplan demonstrated a favorable long-term safety profile and sustained efficacy through to Week E48. High satisfaction rates with self-injection were reported. Funding: UCB Pharma.

**Table: Overview of TEAEs**

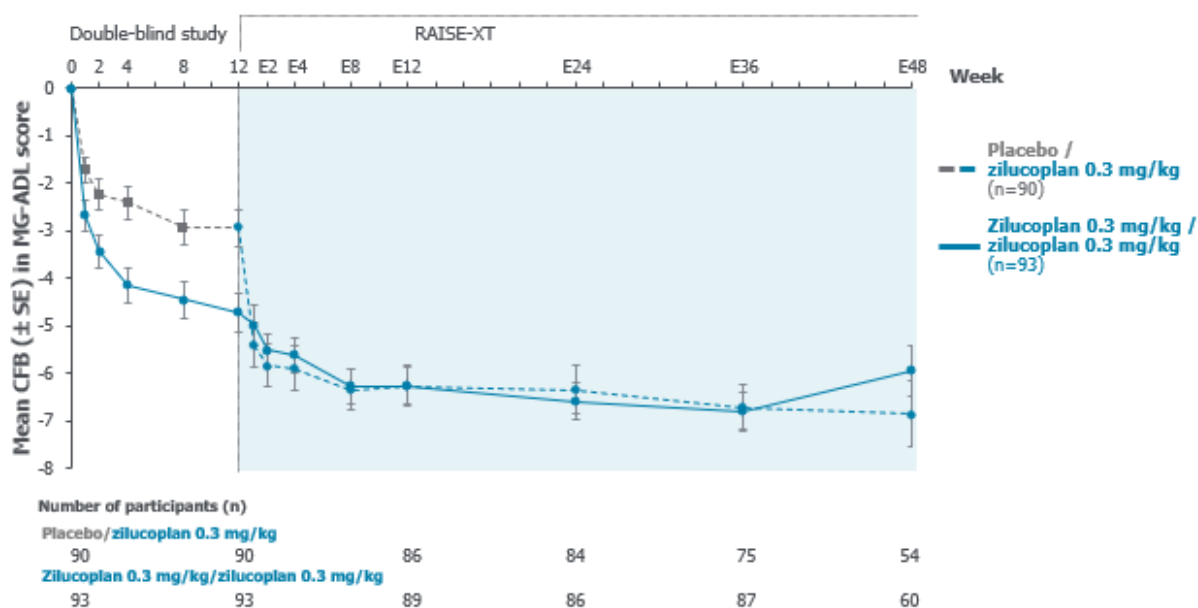
Safety set.

IMP, investigational medicinal product.

	All zilucoplan doses (N=200)
Any TEAE, n (%)	188 (94.0)
Serious TEAE, n (%)	64 (32.0)
TEAE resulting in permanent withdrawal from IMP, n (%)	17 (8.5)
Treatment-related TEAE, n (%)	67 (33.5)
Severe TEAE, n (%)	57 (28.5)
TEAEs leading to death, n (%)	4 (2.0)

**Figure 1: Mean CFB in MG-ADL score to Week E48**

mITT population. Baseline is defined as the baseline before entering the double-blind study. CFB, change from baseline; MG-ADL, Myasthenia Gravis Activities of Daily Living; mITT, modified intention-to-treat; SE, standard error.

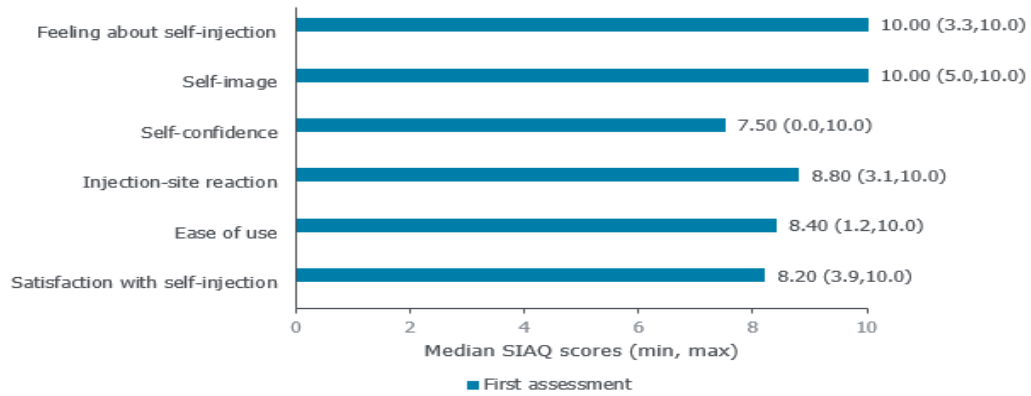


**Figure 2: SIAQ reported outcomes**

All zilucoplan doses, n=63.

For the domain of 'Satisfaction with self-injection', scores  $\geq 8$  are indicative of high or very high satisfaction.

**All zilucoplan doses (n=63)**



## #793- Interim Analysis of Evolve: Evaluating Eteplirsen, Golodirsen, or Casimersen Treatment in Patients <7 Years Old in Routine Clinical Practice

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**Introduction:** Clinical trial 4658-102 (NCT03218995) demonstrated the safety and tolerability of eteplirsen in 6–48-month-old patients with Duchenne muscular dystrophy (DMD).

**Objective:** Describe patients' (<84 months) experience with phosphorodiamidate morpholino oligomer (PMO) treatment (eteplirsen, golodirsen, or casimersen) in routine clinical practice from the ongoing phase 4, observational, EVOLVE study.

**Methods:** Patients were stratified by age at PMO initiation: <24, 24 to <48, and 48 to <84 months. The interim analysis included treatment patterns, safety, and functional assessments.

**Results:** As of December 2021, 32 patients <84 months were enrolled; eteplirsen-treated (n=30): mean (SD) age (years) at treatment initiation was 1.8 (0.05), 3.3 (0.42), and 5.7 (0.74), and mean (SD) duration (years) was 2.5 (1.45), 2.8 (1.66), and 4.6 (1.54) for the <24-, 24- to <48-, and 48- to <84-month-old groups, respectively. Steroid usage before eteplirsen initiation was 0/3, 1/7 (14.3%), and 12/20 (60.0%) for the 3 age groups. Three serious adverse events (SAEs) occurred in 2/30 (6.7%) eteplirsen-treated patients; none were deemed treatment related. Eteplirsen was well tolerated with no treatment-related discontinuations or interruptions. Two patients, 1 golodirsen-treated and 1 casimersen-treated, were enrolled (ages 6.4 and 6.2 years at PMO initiation, respectively; treatment duration was 0.7 years for each). Neither had prior steroid use nor reported SAEs.

**Conclusion:** These real-world data are consistent with the safety of previous clinical studies and further support early initiation of PMOs in young patients.

**Sponsorship:** This study was funded by Sarepta Therapeutics, Inc.

**Disclosures:** **SG, SS, IS, JK:** Employees of Sarepta Therapeutics, Inc. **MAW:** Received research funding as site or study principal investigator from Sarepta Therapeutics, Inc., Novartis Gene Therapies, and Alcyone Therapeutics, Inc., and serves as consultant for Sarepta Therapeutics, Inc. **KM:** Received research support as site principal investigator from Sarepta Therapeutics, Inc., Italfarmaco, Retrotope, Reata, Catabasis, and Santhera Pharmaceuticals, and received research support from NIH (5 U54 NS053672, U24 NS-10718), CDC (U01 DD001248), and FARA. **FA:** Served on advisory boards for NS Pharma, PTC Therapeutics, Santhera Pharmaceuticals, Mallinckrodt, and Sarepta Therapeutics, Inc. **LMRP:** Served on advisory boards for NS Pharma, PTC Therapeutics, Santhera Pharmaceuticals, Mallinckrodt, and Sarepta Therapeutics, Inc., and received research support as principal investigator from Capricor, PTC Therapeutics, Catabasis, Fibrogen, Santhera Pharmaceuticals, and Sarepta Therapeutics, Inc. **RS:** Received research funding from Genentech, Sarepta Therapeutics, Inc., Novartis, Fibrogen, Capricor, argenx BVBA, and Biohaven. **CZ:** Received research support from Biogen and Novartis, served on advisory boards for Biogen, Optum, and Sarepta Therapeutics, Inc. **CM:** Serves as consultant for Astellas/Mitobridge, Bristol Myers Squibb, Capricor, Catabasis Pharmaceuticals, Edgewise Therapeutics, Eli Lilly, Epirium Bio (formerly Cardero Therapeutics), Gilead, Halo Therapeutics, Italfarmaco, Novartis, Pfizer, Prosensa, PTC Therapeutics, Santhera Pharmaceuticals, and Sarepta Therapeutics, Inc., and receives research funding and speaking fees from Sarepta Therapeutics, Inc.

**Prior Presentation:** MDA Clinical and Scientific Conference, 2023; 28<sup>th</sup> International Annual Congress of the World Muscle Society, 2023



## #795- Patient satisfaction following Phase I and Phase II/III primary mitochondrial myopathy trials

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**Introduction:** Primary mitochondrial myopathies (PMMs) are emerging as a major target for drug development. However, inherent challenges to trial design in this group of rare disease remain. Increasingly, patient preference concerning symptom management is used to inform trial design. Nevertheless, there is limited data for patient-reported experience during participation in PMM drug studies.

**Objective:** To explore patient satisfaction during Phase I and Phase II/III clinical trials in PMMs.

**Methods:** Data was collected from people with PMMs who had previously participated in Phase I and Phase II/III clinical trials at The National Hospital for Neurology and Neurosurgery, using a patient-administered survey with the Likert scale 0-10.

**Results:** Seventeen participants responded. Mean age was 55.9 years. The main reason provided for joining a trial was to improve health outcomes in others. The least important factor was receiving compensation for participating. The most burdensome factor was traveling to site while the least burdensome was too much contact with the study team. Seventy one per cent of participants considered questionnaires, and 65% thought assessments, were relevant to PMMs. Weekend visits were suggested to improve accessibility compared with home/remote visits. Nineteen per cent of participants received information about publications and 22% had received information on whether they had the drug or placebo post-trial.

**Conclusion:** Improved accessibility could potentially enable a more diverse PMM population to participate in clinical trials. There is also an opportunity for assessments and questionnaires to be more relevant to participants with PMM. Nevertheless, overall satisfaction was rated high for trial visits.

## #748- Safety and Tolerability of Phenylbutyrate in Inclusion Body Myositis

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**Introduction:** Phenylbutyrate (PBA) showed positive effect on the muscle cell model of Inclusion Body Myositis (IBM) by improving lysosomal activity, ameliorating consequences of impaired autophagy, and decreasing vacuolization. This provides rationale to study this medication in patients with IBM.

**Objectives:** To evaluate the safety and tolerability of phenylbutyrate in IBM and monitor for any early signal of effectiveness.

**Methods:** Open-label study of 10 subjects with IBM who received treatment with PBA for 3 months after a 3 month run-in period. The PBA dose was 3 gm twice daily. The primary outcome measure was adverse event reporting. Secondary outcome measures included manual muscle testing, timed up and go test, IBM functional rating scale, and grip strength, along with exploratory biomarkers evaluating the mitochondrial function, stress response, degenerative process and apoptosis.

**Results:** Ten subjects completed the study. PBA was well tolerated with no serious adverse events related to it. The most common adverse events were GI related and did not require stopping treatment. One of the biomarkers (MitoTracker) showed a statistically significant drop over the treatment period of the study ( $p$ -value of 0.03 for the mean change). There were no statistically significant changes in other secondary outcome measures, but the study was limited by a small sample size and short treatment period.

**Conclusions:** Phenylbutyrate was safe and well tolerated in patients with IBM in this pilot study. The change in the MitoTracker suggests target engagement, but a Phase II study is needed to confirm and study the efficacy of PBA in IBM

#767- A systematic review and meta-analysis of the placebo effect in inclusion body myositis

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**Introduction:** Inclusion body myositis (IBM) is characterized by slowly progressive muscle weakness, making it challenging to detect clinically-meaningful changes in motor function in prospective interventional clinical trials. Furthermore, medical, psychological, and logistic factors may impact trial outcomes, and are grouped under the term “placebo effect”.

**Objectives:** To quantify the change in motor function of IBM patients receiving placebo during prospective interventional clinical trials.

**Methods:** Systematic review and meta-analysis according to the PRISMA guidelines. A comprehensive search of several databases was performed to identify randomized placebo-controlled trials that reported motor outcome measures in the placebo group. Change from baseline was used for effect size, and was converted to standardized mean differences (SMD). DerSimonian-Laird continuous random effect model was used to combine SMD from the different studies. Meta-regression analysis was performed to detect change over time. Heterogeneity was evaluated using the I<sup>2</sup> indicator.

**Results:** 10 eligible studies were identified with overall a low risk of bias. During the trial period, participants with IBM receiving placebo had a measurable decline in their motor function, with SMD of -0.341 (95% CI: -0.624, -0.057;  $p=0.018$ ). Heterogeneity was acceptable ( $I^2=36.9%$ ,  $p=0.113$ ). Meta-regression equation for change in SMD over time (measured in weeks) was:  $SMD = 0.179 - 0.015 \times \text{Follow-up time}$  ( $p=0.028$ ).

**Conclusions:** Patients with IBM displayed measurable decline in their motor function during clinical trials period. Meta-regression equation can help estimating decline in motor function over time.

## #787- The effect of corticosteroid treatment on cardiac function in adults with Duchenne Muscular Dystrophy

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**Introduction:** Duchenne Muscular Dystrophy (DMD) is a progressive genetic disorder of skeletal muscles resulting in muscle degeneration, loss of ambulation in early adolescence and premature death due to cardiorespiratory complications. While the rate at which cardiomyopathy (CM) progresses in corticosteroid (CS) Naïve patients is understood, there is an ongoing debate regarding the extent of protection provided by CS.

**Objectives:** To evaluate the effect of continuing CS treatment on cardiac function in adults with DMD.

**Methods:** A retrospective case note review was conducted at the National Hospital in London, Queen Square. Data on cardiac function and age at start of cardioprotective medication was collected. Patients were stratified into 3 groups: CS Naïve (never had CS or CS treatment <12 months), CS stopped (CS >12 months but stopped prior to transition to adult services) and CS continued (CS continued into adulthood).

**Results:** Data were collected between February 2020 and July 2022. 149 patients were included (77 CS continued, 31 CS stopped, 41 CS Naïve). Mean age at the last assessment was 21.34 ( $\pm 2.70$ ) in CS continued, 22.34 ( $\pm 4.10$ ) in CS stopped and 24.40 ( $\pm 4.82$ ) in CS Naïve group. Age at CM onset (defined as Left Ventricular Ejection Fraction (LVEF) <45% or Left Ventricular Fraction Shortening (LVFS) <28%) was 12.77y ( $\pm 3.79$ ) in CS continued (N=25), 13.13y ( $\pm 3.23$ ) in CS stopped (N=16) and 14.34y ( $\pm 2.59$ ) in CS Naïve (N=18). All individuals were on variety of cardioprotective medications.

**Conclusions:** Longitudinal data of LVEF and LVFS and other statistical analyses are in progress and will be presented and results discussed.

#718- Effectiveness of conservative non-pharmacological interventions in people with muscular dystrophies (MD): a systematic review and meta-analysis

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**Introduction:** Muscular dystrophies (MD) are managed with conservative non-pharmacological interventions, but evidence of their effectiveness is limited.

**Objective:** To investigate the effectiveness of such interventions for MD physical management.

**Methods:** PRISMA guidelines were followed. MEDLINE, CINHAL, Embase, AMED and CENTRAL (inception to August 2022) were searched. Effect size (ES) and 95% confidence intervals quantified treatment effect.

**Results:** Of 31,285 identified articles, 39 studies (957 participants), mostly at high risk of bias, were included. For children with Duchenne muscular dystrophy (DMD), trunk-oriented strength exercises and usual care were more effective than usual care alone in improving distal upper-limb function, sitting and dynamic balance; physiotherapy plus aerobic treadmill training was more effective than physiotherapy plus-ergometer training for anterior-posterior stability; arm ergometer training was more effective than range-of-motion exercises for arm elevation movement quality. For adults with Facioscapulohumeral dystrophy (FSHD), Limb-girdle muscular dystrophy (LGMD) and Becker muscular dystrophy (BMD), strength-training improved dynamic balance and self-perceived physical condition. A multicomponent program improved gait in adults with Myotonic dystrophy type 1 (DMI). ESs varied from -1.26 to 2.29.

**Conclusions:** Strength-training, with or without other forms of exercise, may improve function and well-being in MD. Although evidence quality was low, strength-training should be considered in MD management, as it was found to be safe.

## #735- Mycophenolate is better tolerated than azathioprine in myasthenia gravis

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<sup>1</sup>The Northern Care Alliance NHS Foundation Trust; <sup>2</sup>The University of Manchester; <sup>3</sup>Newcastle Hospitals NHS Foundation Trust; <sup>4</sup>The Walton Centre NHS Foundation Trust; <sup>5</sup>Nottingham University Hospitals NHS Foundation Trust; <sup>6</sup>University Hospitals Birmingham; <sup>7</sup>University College London Hospitals NHS Foundation Trust; <sup>8</sup>Imperial College Healthcare NHS Trust; <sup>9</sup>Oxford University Hospitals NHS Foundation Trust.

**Introduction:** Azathioprine is generally considered the first-line steroid-sparing immunosuppressive agent for myasthenia gravis (MG). Mycophenolate and methotrexate are often reserved as second-line choices due to lack of randomised controlled trial evidence, despite widespread consensus on their efficacy.

**Objectives:** We aimed to gather real-world data on the side effects of steroid sparing agents, their use in United Kingdom (UK) clinical practice, and the reasons for discontinuation in the UK.

**Methods:** We performed a national survey of side effects and reasons for discontinuation of immunosuppressants in patient with MG in the UK. 235 patients who completed the survey; 166 had taken azathioprine, 102 mycophenolate, and 40 methotrexate.

**Results:** High proportions of patients reported side effects from their medications for MG; 90% of those on prednisolone, 79% pyridostigmine, 78% azathioprine, 62% methotrexate, and 60% mycophenolate. Side effects of treatments for MG led to admission to accident and emergency (n=7) or hospital (n=33) in 17% of patients.

Azathioprine was discontinued by 66% of patients who started it (53% of these due to side effects), compared to only 19% mycophenolate (26%), and 32% methotrexate (25%). Azathioprine was significantly more likely to be discontinued than mycophenolate due to side effects ( $p < 0.0001$ ). There was no significant difference in treatment cessation due to lack of effect.

**Conclusions:** This real world data highlights the significant burden of treatment for MG. Mycophenolate appears to be better tolerated than azathioprine. Strategies to optimise azathioprine dosing such as azathioprine metabolite testing should be utilized to reduce the risk of treatment failure.

## Stratification of NMD & Disease Burden

### #740- Compound Muscle Action Potential Amplitude as a Biomarker of Myasthenia Gravis

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**Introduction:** Myasthenia gravis (MG) is an autoimmune disorder that results in failure of the neuromuscular junction (NMJ). Compound muscle action potential (CMAP) is an electrodiagnostic (EDX) test that measures muscle excitation after nerve stimulation, and reduced CMAP amplitude during repetitive nerve stimulation (RNS) is a standard diagnostic test for MG. Single fiber electromyography (SFEMG) is another EDX test that is more sensitive but less commonly used.

**Objectives:** To explore correlations between clinical severity, serological titers, and EDX profiles in MG.

**Methods:** A chart review of patients aged >18 years with an MG diagnosis to analyze acetylcholine antibody titer (AChR), EDX results (CMAP, RNS, SFEMG) of hand, trapezius, and facial muscles, and MG Foundation of America (MGFA) clinical severity.

**Results:** 18 male, 34 female (55 +/- 16 years, range: 20-81 years) were categorized into ocular-MGFA 1, mild generalized-MGFA 2, and moderate-severe generalized-MGFA 3-5 groups. CMAPs exhibited differences between MGFA groups, indicating smaller CMAPs with more severe MG (one-way ANOVA,  $p < 0.05$ ). RNS and SFEMG results were similar across groups. AChR titers were comparable between MGFA groups and negatively correlated with average RNS decrement (Spearman,  $p < 0.05$ ), but not with CMAP or SFEMG.

**Conclusions:** Correlation between MGFA and CMAP, but not other standard MG diagnostic tests (RNS, SFEMG), may suggest that functional impairment in MG may be driven by the accumulation of static rather than variable NMJ failure. AChR and RNS decrement showed a correlation, implying a relationship between AChR and variable NMJ failure. Prospective studies could investigate CMAP as a biomarker for MG.

## #776- Burden of Myasthenia Gravis (MG) Based on Sentiment Analysis of Patients' Digital Conversations

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**Introduction:** MG is a rare, chronic autoantibody neuromuscular disease with profound patient burden. Data from digital conversations can highlight areas most concerning to patients.

**Objectives:** To describe sentiments towards MG and compare males vs females on the most frequent themes.

**Methods:** One year [8/2021–8/2022) of MG-focused public domain conversations from US internet protocol addresses were tagged based on self-identification in the conversations or public profiles. Advanced search techniques and artificial intelligence powered algorithms were used to extract and organize data by topics into an unstructured dataset. Sentiment analysis via natural language processing was used to classify conversations as positive, negative or neutral and analyzed to derive the most frequent drivers of sentiment.

**Results:** Of 13,234 conversations (from topical sites, message boards, social networks and blogs), the most frequent conversation topic categories were diagnosis (29%), living with MG (28%), symptoms, (24%) and treatment (19%). Of 3176 conversations on symptoms, eye problems (21%), facial muscle problems (18%), and fatigue (18%) featured most frequently. Most conversations (59%) were negative in tone and meaning, 39% were neutral and only 2% were positive. Negative conversations were dominated by themes of impact on life (29%), misdiagnosis problems (27%), treatment issues (24%), and symptom severity (20%). Males had more conversations with negative sentiment vs females while females seemed more pragmatic in their outlook on MG.

**Conclusions:** Digital conversations reveal a high degree of concern among patients with MG most specifically related to symptoms, life impact, misdiagnosis and MG treatments. Therapies providing better symptom control could positively affect many aspects of patient's lives.



## #770- Remote Monitoring and Management of Myasthenia Gravis (REMOTE-MG): A Pilot Feasibility Study

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**Introduction:** Time while myasthenia gravis (MG) patients are symptomatic is critical due to inability to work, perform activities of daily living, or care for families. MG patients are often evaluated every 3 – 6 months. Physicians are blind to fluctuations in patient function between visits unless patients call to report changes. Given the national shortage of neurologists, more frequent follow-up is not feasible.

**Objectives:** Evaluate the feasibility and utility of measuring MG patient symptoms using a web-based or app-based MG monitoring system.

**Methods:** We designed a prototype remote monitoring tool in REDCap; the tool measures MG-ADL, MG-QOL15r, global visual analogue scale, patient acceptable symptom state, and presence/absence of side effects. Enrolled MG patients (target N=50) in the Northern New England Clinical and Translational Research Network (Vermont, Northern New York, and Maine) will remotely report MG symptoms weekly for 8 weeks. The primary outcome is  $\geq 75\%$  patient completion rate and  $\geq 75\%$  secure transfer of data to treating physicians. Change in treatment plan based on data is an exploratory outcome.

**Results:** 10 patients are currently enrolled. Preliminary study results and study design will be presented.

**Discussion:** Given the fluctuating nature of MG, prolonged periods of treatment adjustments, shortage of neuromuscular physicians, now is the time to revolutionize MG care and pivot to a care model adapted for the current times and technology. If this study is successful, a future protocol to act on remotely collected data will be designed with an ultimate goal of reducing time with symptoms for MG patients.

## #771- Measuring Adverse Event Burden in Myasthenia Gravis: Retrospective Validation of the Adverse Event Unit (AEU) with MGTX Trial Data

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**Introduction:** The Adverse Event Unit (AEU) is a patient and physician weighted consensus unit that quantifies and compares adverse event (AE) burden among any group of medications in neurologic patients. A recent single-center, prospective, study demonstrated feasibility and preliminary validity of utilizing the AEU to measure AE burden in myasthenia gravis (MG).

**Objectives:** Evaluate feasibility of assigning AEU scores retrospectively from AE data recorded in the MGTX randomized trial of thymectomy in MG. Quantify differences in AE burden utilizing the AEU in MGTX trial participants treated with different dosages of prednisone.

**Methods:** Serious and non-serious AE were recorded at all MGTX visits. AEU scores were assigned by matching each MGTX AE to the best matched category in the AEU scale; death and MG worsening were not coded as side effects. AEU scores will be compared among participants receiving varied doses of prednisone and for participants receiving prednisone for different durations.

**Results:** The MGTX trial randomized 126 patients at 36 sites. All patients received prednisone; prednisone dosage was adjusted during the trial. Non-severe AE were reported at 747/2187 (34%) of study visits (Median AEU score 3 IQR 3-7). Severe AE were reported at 46 study visits (2%) (Median AEU score 7.5 IQR 7-12).

**Discussion:** This study demonstrates feasibility of assigning AEU scores retrospectively from clinical trial data. MGTX Median AEU scores are similar to UVM prospective study MG median AEU score (5 IQR 0-8). AEU scores in relation to prednisone dose and thymectomy status will be presented.

## #727- Treatment Preferences of Patients with Myasthenia Gravis

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**Introduction:** The patient burden of MG is often underestimated. New MG treatments, such as biologics, may increase the proportion of patient symptom-free patients. However, these new treatments have potential side effects and associated costs. Understanding the treatment preferences of people with MG will help inform patients, clinicians, and policy makers.

**Objectives:** We aim to study how people with MG make decisions regarding new interventions--considering trade-offs between potential side effects and efficacy.

**Methods:** Fifteen patients with a wide range of MG severity participated in semi-structured interviews. Interviews were recorded and transcripts were analyzed using line-by-line open coding, to generate themes. We used these themes to identify treatment characteristics to develop a discrete choice experiment to study how people with MG make treatment decisions.

**Results:** Four themes were identified: MG symptoms and burdens, patient experience with treatment side effects, patient treatment preferences and patient treatment goals. Most patients preferred treatments in the form of pills (67%). The greatest reported treatment goals were returning to normal or zero symptoms (40%), discontinuation of prednisone (40%), and a preference to take less pills (33%). Double vision was the most bothersome symptom for 33% of patients and 33% reported weight gain as the most bothersome side effect.

**Conclusion:** We identified relevant characteristics for potential MG treatments. The attributes for the ongoing discrete choice experiment are: improvement in eye function, improvement in bulbar symptoms, improvements in arms/legs function, ability to reduce prednisone dose, risk of infections, administration mode, and out-of-pocket cost to estimate willingness to pay.

## #779- Summated Compound Muscle Action Potential Amplitude as a Biomarker of Amyotrophic Lateral Sclerosis

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**Introduction:** With the evolving amyotrophic lateral sclerosis (ALS) therapeutic landscape, there is a growing need for diagnostic, prognostic, and treatment response biomarkers.

**Objectives:** The aim of this study was to explore summated compound muscle action potential amplitude (CMAP) as a candidate biomarker.

**Methods:** ALS patients (El Escorial definite and probable) were recruited at diagnosis. Bilateral median, ulnar, peroneal, and tibial nerves CMAPs were assessed as individual and summated values and compared with other clinical ALS assessments. A small healthy control cohort was included for CMAP comparison.

**Results:** Forty ALS patients (21 males, 19 females, mean age of  $55.9 \pm 12.8$  years) and controls (3 males, 3 females, mean age of  $33.2 \pm 3.4$  years) were enrolled. Mean duration (symptom onset to diagnosis) was  $7.9 \pm 5.2$  months, and the ALS Functional Rating Scale-revised (ALSFRS-R) was  $37 \pm 7.6$ . Summated CMAP was significantly reduced (>40%) in ALS versus controls ( $36.2 \pm 13.9$  vs.  $63.7 \pm 11.2$ ,  $p < 0.0001$ ) and similarly all individual CMAPs were significantly reduced ( $p < 0.05$ ) except for the left tibial motor ( $p=0.14$ ). Summated CMAP correlated with ALSFRS-R, total manual muscle testing score, and disease duration ( $r = 0.36$ ,  $p = 0.023$ ; and  $r = 0.32$ ,  $p = 0.045$ , and  $r = -0.33$ ,  $p = 0.039$ , respectively).

**Conclusions:** Most individual CMAP responses were reduced indicating significant generalized lower motor neuron disease burden at time of diagnosis. Summated CMAP could be a potential biomarker of ALS, and future studies should investigate change longitudinally and with therapeutic interventions.

## #783- Factors Influencing Genetic Testing Uptake in Amyotrophic Lateral Sclerosis (ALS) Patients

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Amyotrophic lateral sclerosis (ALS) is a debilitating neurodegenerative disease, and the role of genetic counseling and testing in ALS clinics remains underexplored. This study aimed to assess the value of incorporating genetic counseling and testing in a multidisciplinary ALS clinic and identify factors influencing the uptake of genetic testing.

A chart review was conducted to gather clinical and demographic data of ALS patients seen at MUSC between July 1, 2021, and July 1, 2023, who were offered genetic testing. Additionally, a survey was sent to 60 living patients to assess their decision to undergo genetic testing and rate the importance of various factors on a scale of 1 to 5.

Out of the 24 respondents (40% response rate), 17 patients (70.83%) underwent genetic testing, while 7 patients (29.17%) did not. Participants who underwent genetic testing consistently rated the influencing factors higher than those who did not. In Group 1, the most important factor was family risk assessment (median: 5), followed by clarity regarding the disease's origin and diagnosis confirmation. Similarly, in Group 2, family risk assessment ranked highest (median: 1), even among those who chose not to undergo genetic testing.

These findings emphasize the perceived significance of family risk assessment in decision-making related to genetic testing for ALS. The study underscores the potential value of integrating genetic counseling and testing into multidisciplinary ALS clinics, providing insights for healthcare professionals, genetic counselors, and researchers involved in ALS care.

Further analysis is ongoing, and this study contributes to our understanding of the factors influencing the decision to undergo genetic testing in ALS patients. The results hold implications for improving ALS diagnosis, treatment, and patient support by considering the factors that influence genetic testing uptake.

#761- Utility of genetic panels for neuromuscular disorders in a tertiary referral center neurology clinic in Central Pennsylvania

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**Introduction:** Genetic testing panels have become frequently utilized in the neurology clinic. Recent AANEM guidelines state these tests are essential to diagnosis of a neuromuscular disease. Despite the overall benefit in uncovering a genetic diagnosis, previous studies have shown a wide range in utility.

**Objectives:** Our aims are to determine our yield from genetic panel testing, uncover specific patient presentation patterns and diagnostic studies to aid in genetic testing.

**Methods:** Data will be collected from a single site, tertiary referral center in central Pennsylvania. Gene panel results from Invitae (San Francisco, California) and GeneDx (Gaithersburg, Maryland) of roughly 900 patients will be evaluated in correlation with demographic data, presentation, family history, and electrodiagnostic (EDX) studies.

**Results:** Preliminary data comprising results of 109 patients were categorized based on presenting symptoms as follows: myopathic 21.1%, neuropathic 24.8%, motor neuron disease 29.4%, upper motor neuron 2.8%, other 29.4% which is comprised of vague muscle weakness, muscle stiffness/cramps, small fiber neuropathy, dysautonomia, hyperCKemia, referral for genetic symptoms in asymptomatic patients. Of those presenting with neuropathic, myopathic, and motor neuron features with a positive gene panel result, 60%, 50%, and 100% respectively had a positive family history/electrodiagnostic study compared to uncertain results with 2%, 15%, and 12% for positive family history and 36%, 15%, and 88% for positive electrodiagnostics.

**Conclusions:** Preliminary data demonstrates a greater percentage of positive gene panel results with positive family history and EDX. This data collection will enable the development of an algorithmic approach for genetic testing based on phenotypic presentation, family history, and EDX studies.

#755- Relationships of Lower Leg Fat Fraction among antagonistic and synergistic muscles and a potential Fat Fraction threshold for functional performance in Myotonic Dystrophy Type 1

Zhihao He, Aruna Thomas, Yuting Luo, Naphlim Olwe, Samuel Riehl, Eric Wang, Krista Vandenborne, Glenn A. Walter, SH Subramony, Donovan J. Lott

**Introduction:** Quantitative Magnetic Resonance Imaging (qMRI) is an objective, sensitive tool for assessing fat fraction (FF) in patients with Myotonic Dystrophy Type 1 (DM1). However, no research has explored the correlation of FF in antagonistic and synergistic muscles and the impact of FF on functional tests.

**Objective:** To investigate the relationships of lower leg FF in antagonistic and synergistic muscles in DM1, the effect of FF on functional mobility, and if there is a threshold for FF to distinguish between functional performance.

**Methods:** Eighteen ambulatory, adult DM1 subjects (11 females) were tested. FF was determined via qMRI for six lower leg muscles from Dixon imaging using a 3T scanner, and mobility was assessed via various walking tests. Associations were identified via correlation coefficients. We also examined the performance in mobility based on FF to investigate whether a threshold could be defined to discriminate functional abilities.

**Results:** Strong correlations were found between FF in the antagonist ( $r=0.77$ ) and synergist groups ( $r=0.80-0.89$ ) of the lower leg. FF of the lower leg muscles also correlated with walking and mobility tests ( $r=0.61-0.90$ ). Lower leg FF of 0.2 appeared to discriminate for functional mobility performance.

**Conclusions:** Strong relationships between lower leg muscle FF may be more indicative of the disease process affecting all lower leg muscles rather than selective involvement based upon muscular function. qMRI used to assess lower leg FF revealed that 0.2 appears to be a potential threshold for functional abilities in DM1 patients that should be explored further in future studies.

#821- USE OF GAS SCALE TO IDENTIFY RELEVANT CENTRAL NERVOUS SYSTEM DOMAINS IN MYOTONIC DYSTROPHY TYPE 1: DIAGNOSTIC AND OUTCOME MEASURE PROSPECTIVE FOR CLINICAL CARE AND TRIALS

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**Introduction:** Myotonic Dystrophy Type 1 (DM1) is a multisystem disorder, and central nervous system (CNS) dysfunction is one of its core and most heterogeneous clinical manifestations. Heterogeneity and multi-domain involvement make CNS functions assessment challenging, and – despite the progress made – current tests and scales neither can detect what is clinically relevant and matters to the patient nor can capture changes over time. The Goal Attainment Scale (GAS) is a validated scale centered on patient's goals, offering an opportunity to reflect clinically meaningful data which are individualized and potentially useful to derive a semi-quantitative patient-generated outcome.

**Objectives:** The aim of this study is to explore the use of a revised version of the GAS in DM1 as a potential patient-centered semi-quantitative outcome measure to engage patients, measure clinically meaningful changes and monitor patients perception of change over time.

**Methods:** Patients who underwent a full battery of validated patient-reported outcome measures (PROMs) in the last year were recruited. The GAS scale was revised and adapted for DM1.

**Results:** 73 adult patients (median age 45 [39 – 53], median MIRS 4 [4 – 4]) were recruited, 5 different SMART goals were identified: 1. cognitive impairment with executive dysfunction and lack of attention, 2. visuospatial deficits 3. social dysfunction, 4. personality abnormalities and 5. excessive daytime sleepiness (EDS) and fatigue. Data are under analysis.

**Conclusions:** Assessment, data collection and monitoring can be challenging when it comes to CNS in DM1: ongoing analysis will provide insight about GAS adequacy and consistency in this field.



## #789- Natural history of pulmonary function in adult patients with Spinal Muscular Atrophy type 2 and 3

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**Introduction:** The respiratory natural history in adult patients with Spinal muscular atrophy (SMA), particularly relevant considering the availability of disease-modifying treatments, is currently undefined.

**Objectives:** To describe the annual progression of pulmonary function (forced vital capacity, FVC) and non-invasive ventilation (NIV) requirement across in adults with SMA type 2 and 3.

**Methods:** Retrospective observational natural history study of adult patients followed by five Italian centres and by one US centre of the International SMA Consortium (iSMAC).

Patients' anthropometrics, FVC absolute, FVC% pred., NIV requirement were collected.

**Results:** One hundred seventy-four patients were included. The median follow-up duration was 38.3 months. Seventy-four were SMA type 2, median (IQR) age was 25.9(19.2-35.3). One hundred were SMA type 3, median (IQR) age was 35.5(24.4-45.2).

SMA type 2 had a significantly lower FVC absolute (0.9 vs 3 L,  $p < 0.0001$ ), FVC% pred. (28 vs 87%,  $p < 0.0001$ ) and PCF (145 vs 361 l/min,  $p < 0.0001$ ) than SMA type 3 at first assessment. Respiratory function significantly differed across motor functional status groups within SMA type 2 and 3.

FVC% progressed annually by 0.10% and 0.48% in SMA type 2 and 3, respectively and did not differ according to motor functional groups suggesting stability.

Conversely, due to the different lung volumes at first assessment, the median age when FVC% pred. fell below 60%, 40% and 20% was significantly lower in SMA type 2 than type 3.

**Conclusions:** These novel results will serve as benchmark to assess the impact of disease-modifying treatments in the adult SMA population.

#803- Scoliosis progression in type II SMA at the time of treatment: a comparative study with untreated patients

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**Introduction:** Scoliosis is a significant complication in individuals with Type II Spinal Muscular Atrophy (SMA), affecting their quality of life. While pharmacological treatments have demonstrated efficacy in improving motor and respiratory function in type II SMA, there is limited information available regarding their impact on scoliosis.

**Objective:** The objective of this prospective study was to examine the impact of pharmacological treatment on scoliosis progression in Type II SMA patients and compare it to untreated individuals.

**Methods:** Treatment effect on Cobb's angle annual changes and on reaching a 50° Cobb angle was analysed in treated and untreated Type II SMA patients with a minimum 1.5-year follow-up. A sliding cut-off approach identified the optimal treatment subpopulation based on age, Cobb angle, and HFMSE at the initial visit.

**Results:** No significant difference was found in mean Cobb variation between untreated (n=46) and treated (n=39) groups (p=0.4). Optimal cut-off values for a better outcome were Cobb angle <26° and age <4.5 years. In this resampled population, the untreated group had a mean Cobb variation of 10.05 (SD 6.38) degrees/year, while the treated group had 5.61 (SD 4.72) degrees/year (p=0.01). Cox regression analysis indicated a protective treatment effect in reaching a 50° Cobb angle, significant in patients <4.5 years old (p=0.016).

**Conclusions:** This study highlights that pharmacological treatment, if initiated early, may slow down the progression of scoliosis in Type II SMA patients. Larger studies are warranted to further investigate the effectiveness of individual pharmacological treatment on scoliosis progression in this patient population.

## #797- Assessment of Patient-Reported Physical Fatigue in Spinal Muscular Atrophy (SMA): Insights from a Pilot Study

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**Introduction:** Fatigue is a disabling symptom in SMA routinely assessed with multidimensional patient-reported outcome measures (PROMs). The current approach to perceived fatigue assessment eludes meaningful association with performance due to current multidimensional methods and disease confounders. Perceived fatigability, a whole-body measure of experienced physical fatigue, has not been studied in SMA.

**Objective(s):** Develop an SMA-specific PROM to measure perceived fatigability.

**Methods:** English-speaking individuals across three international SMA registries, ≥12 years with confirmed SMA, completed an anonymized self-survey. The scale included 108 items organized across 33 activity groupings. Experienced or imagined fatigue with current or previously performed activities were rated from 0=No Fatigue to 5=Extreme Fatigue. We identified items that ≥80% of participants reported minimal fatigue (score=0/1) for each functional group.

**Results:** One-hundred and eighteen participants with a mean age of 41.3 years (range 14-78; 48% male; 61% receiving disease-modifying therapy) completed the survey. Current functional status included sitters (45%), non-sitters (40%), and walkers (15%). Forty participants (33%) had achieved walking with or without support but were no longer able to at time of survey.

Minimal fatigue was reported in 2 items for non-sitters, 15 for sitters, and 19 for walkers. On average, participants rated their “usual energy” 6.2 out of 10 (range 0-9) during the past month, with no associations with age, function, or SMA type ( $p>0.05$ ).

**Conclusions:** We developed a perceived fatigability scale, with activity intensity and duration anchors to measure experienced physical fatigue across SMA phenotypes. This may help to elucidate the impact of therapies on subjective patient well-being and function.

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#745 Relationship of autoantibody status in dermatomyositis patients to response to IVIG treatment. A post-hoc analysis of the ProDERM study

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**Introduction:** Dermatomyositis (DM) is an immune-mediated idiopathic inflammatory myopathy (IIM). Two subsets of autoantibodies have been identified in patients with IIM: myositis-specific antibodies (MSA, such as anti-Jo-1, anti-TIF-1 and anti-MDA-5) and myositis-associated antibodies (MAA, such as anti-PM-SCL, anti-Ku and anti-Ro). The ProDERM study recently demonstrated the efficacy and safety of intravenous immunoglobulin (IVIG) in 95 DM patients.

**Objectives and Methods:** In this post-hoc analysis of the randomized, placebo-controlled ProDERM study the autoantibody status at baseline and its relationship to treatment response to IVIG were investigated. Baseline serum samples were analyzed for MSA and MAA by the Oklahoma Medical Research Foundation. Treatment response was measured by TIS (Total Improvement Score).

**Results:** At baseline, 49 (52%) patients were MSA-positive, 13 (14%) MAA-positive, and in 33 (35%) no antibody was detected.

In the MSA group, 71% showed at least minimal TIS response (score  $\geq 20$ ) at week 16, compared to 55% in the “no-autoantibody-detected” group and 38% in the MAA+ group. TIS response was more common in the MSA+ group than the MAA+ group at Week 16 ( $p=0.03$ ).

In the MSA+ group 24 patients were randomized to IVIG and of these 83% showed at least minimal TIS response (score  $\geq 20$ ) at week 16 compared to 60% of the MSA+ patients randomized to placebo.

More data on TIS response in patients with specific MSA autoantibodies (such as anti-TIF-1, antisynthetase or anti-Mi-2) will be presented at the meeting.

**Conclusion:** IVIG appears to be an effective agent for treatment of dermatomyositis, regardless of autoantibody status for the majority of autoantibodies. Further analyses will determine if specific MSA play a role in treatment response to IVIG.

## #819- GETTING READY FOR TRIALS INVESTIGATING DYSPHAGIA DIAGNOSTIC AND OUTCOME MEASURES IN MYOTONIC DYSTROPHY TYPE 1 (DM1): A SINGLE-CENTER RETROSPECTIVE LONGITUDINAL STUDY

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**Introduction:** Pneumonia is the main cause of death in DM1 and aspiration may play an important role. Yet dysphagia is a seldom complaint, is poorly studied in the initial stages of disease and consensus about assessment and management is scanty in this disease.

**Objectives:** The aim of our study was to assess swallowing function of patients with DM1 using a multimodal approach, focusing on the feasibility and consistency of the tests and measures adopted.

**Methods:** Dysphagia was assessed in adult patients with DM1 with fiberoptic endoscopic evaluation (FEES) and validated questionnaires such as the symptom specific semi-quantitative scale Eating Assessment Tool 10 (EAT 10) and the qualitative survey SWAL-Qol.

**Results:** FEES showed that out of 113 patients (mean age: 49 years [42.50 – 57.50], mean disease duration: 16.76 years [9.56 – 23.72]; mean MIRS: 4 [3 – 4]) 27 (24%) had a normal swallowing function (Dysphagia Outcome Severity Scale (DOSS): 6-7), 81 (72%) had mild-moderate impairment (DOSS: 3-5) and 5 (4.5%) had severe impairment (DOSS: 1-2). The EAT-10 score was  $\geq 3$ , indicative of a swallowing involvement, in 65% of the patients, showing good association with the DOSS as the difficulty in swallowing increased. The SWAL-Qol showed a mild association with the DOSS and only for severe dysphagia.

**Conclusion:** Dysphagia had a high prevalence in our cohort and most of our patients showed mild-moderate swallowing impairment. According to the patient-reported questionnaires the awareness of the problem was scarce in the initial stages, and showed only mild association with the endoscopic scale scores with the worsening in the swallowing function, possibly leading to unexpected complications. A multi-modal approach is crucial to evaluate properly swallowing in DM1, and further effort needs to be addressed to patient-reported outcomes due to their potential clinical impact.

#816- Evaluation of ankle reflex and sural sensory nerve action potentials in a large patient cohort with cryptogenic peripheral polyneuropathy

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**Introduction:** Two common initial symptoms for peripheral neuropathy (PN) are a reduced Achilles tendon reflex (ATR) and a reduced sensory nerve action potential (SNAP) of the sural nerve. However, both can also be observed in otherwise healthy older or taller individuals.

**Objectives:** This study aims to investigate the prevalence of absent or reduced ATRs and SNAPs in a large patient cohort with cryptogenic sensory peripheral neuropathy (CSPN).

**Methods:** The records from 829 patients enrolled in the Peripheral Neuropathy Research Registry (PNRR) were evaluated and stratified into five subgroups for age (<50, 50-59, 60-69, 70-79, and ≥80 years) and height (<160, 160-169, 170-179, 180-184, and ≥185 cm) to search for correlations in regard to age, height, age at time of PN onset, PN duration, BMI and other factors that could influence PN-severity

**Results:** The likelihood of an absent ATR was associated with taller ( $p=0.0002$ ) and older subjects ( $p<0.0001$ ). ATR was found to associate with age at the time of symptom onset ( $p<0.0001$ ), time since PN-symptom onset ( $p<0.0001$ ), and height ( $p<0.0001$ ). Sural SNAP was found to be consistently absent in taller ( $p<0.0001$ ) and older subjects ( $p<0.0001$ ), and was associated with age at time of symptom onset ( $p<0.0001$ ), time elapsed since PN-symptom onset ( $p<0.0001$ ), height ( $p<0.0001$ ), and BMI ( $p<0.0001$ ).

**Conclusions:** Age and height both contributed to likelihood of a reduced/absent ATR and sural SNAP. In addition, the time since onset of neuropathy as well as age at the time of onset also increased the likelihood of absent or reduced ATRs and sural SNAPs.

#774- Development of a Novel, Disease-Specific, Patient-Reported Outcome Measure; the Myotonic Dystrophy Type 2 Health Index (MD2HI)

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**Introduction:** There is a need for reliable, sensitive, disease-specific, patient-reported outcome measures capable of detecting clinically relevant changes in myotonic dystrophy type 2 (DM2) disease progression, as well as therapeutic gain over time.

**Objectives:** To develop and validate the Myotonic Dystrophy Type 2 Health Index (MD2HI) for use in DM2 therapeutic trials and clinical monitoring.

**Methods:** We conducted semi-structured qualitative interviews and a cross-sectional study with DM2 patients to determine the most common and impactful symptoms. We selected questions for the first version of the MD2HI based on their relevance, as determined by the cross-sectional study results. We used factor analysis to generate instrument subscales, which measure granular areas of symptomatic health. We performed beta testing to optimize the instrument usability and clarity resulting in the second version of the MD2HI.

**Results:** Fifteen individuals with DM2 participated in qualitative interviews and 74 participants completed the cross-sectional study. Additional individuals with DM2 participated in beta testing and reported that the instrument was straight forward and easy to use. Following beta interviews, modifications were implemented based on participant feedback, resulting in a more efficient version of the MD2HI.

**Conclusions:** The development and validation of the updated MD2HI provides researchers and clinicians with a valid, reliable, and efficient tool to measure relevant changes in DM2 disease burden over time or in response to therapeutic intervention.



## #769- Motor Outcomes to Validate Evaluations in Facioscapulohumeral muscular dystrophy (MOVE FSHD): Preliminary Baseline Characteristics

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The MOVE FSHD study aims to determine the predictive value of clinical and motor assessments, patient-reported outcomes, imaging, and tissue biomarkers on disease progression in FSHD. This comprehensive study is important not only for improving patient care, but to understand what kind of change would be meaningful for clinical trials. Study will evaluate 450 FSHD participants over three years with 200 participating in a MRI and muscle biopsy sub-study to validate FSHD evaluations. Annual visits collect FSHD history, physical examination, patient reported outcomes, strength, timed functional tasks, and respiratory parameters. Sub-study participants will have additional biomarkers collected, including reachable workspace at every visit, whole body MRI at Baseline and 12-Month visits, muscle biopsy at Baseline and at 4-months (n=40). The MOVE FSHD study has over 240 participants who have completed their Baseline visit, more than 140 have returned for annual follow-up visits and sites have also begun enrolling MOVE+ sub-study participants. Our cohort is predominantly non-Hispanic white with 58% being male, 88% FSHD Type 1, and 92% are ambulatory. We currently have 12 individuals enrolled under the age of 18. Lastly, more than 50 of our previous 161 US participants from the ReSolve FSHD study have enrolled in the MOVE study with the remainder expected to roll-over within the next 1-2 years. MOVE FSHD addresses barriers to clinical trials by validating motor, clinical, and patient reported outcomes, as well as potential biomarkers. The data from MOVE FSHD can also improve our understanding of FSHD and directly impact patient care.

**Funders:** Grants from FSHD Society, Friends of FSH Research, FSHD Canada, and Avidity Biosciences.

**Reference:** Statland JM, Tawil R. Facioscapulohumeral Muscular Dystrophy. *Continuum (Minneapolis)*. 2016;22(6, Muscle and Neuromuscular Junction Disorders):1916-31. Epub 2016/12/07. doi: 10.1212/CON.0000000000000399. PubMed PMID: 27922500; PMCID: PMC5898965.

## #820- Examining Recovery from Maximal Exercise Testing in Patients with Neuromuscular Disease

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**Introduction:** Patients with neuromuscular diseases (NMD) have decreased physical activity increasing the risk of cardiovascular and pulmonary disease. Assessing cardiorespiratory fitness via cardiopulmonary exercise testing (CPET) is an important factor in determining exercise and functional capacity. Evaluating recovery kinematics can provide insight into disease mechanisms and recovery from activity.

**Objectives:** The objective of the study is to evaluate recovery metrics in NMD compared to controls.

**Methods:** This is a prospective study in individuals with NMD and controls. CPET was performed using a Cosmed K5 metabolic system and a wheelchair-accessible Keiser M7i total body trainer. Recovery was defined as the period when workload ended until participants returned to within 10% of resting heart rate and oxygen consumption. Analysis on recovery metrics was performed at the time of 50% peak oxygen after peakVO<sub>2</sub> (T<sub>1/2</sub>) over a duration of 3 minutes.

**Results:** Forty-nine participants were included: 15 controls and 34 NMD. The 34 participants with NMD were recruited from the Stanford Neuroscience Health Center. No significant demographic differences were found between groups. Peak exercise variables showed significant differences between groups, with controls demonstrating higher values. NMD had longer recovery times for oxygen, lower overshoot values for respiratory exchange ratio and ventilation/VO<sub>2</sub>.

**Conclusion:** NMD demonstrates different recovery metrics post CPET compared to controls. Results indicate impairments in recovery in patients with NMD, demonstrating limitations in exercise capacity and recovery. Understanding differences in recovery can optimize exercise prescriptions, improve prognostication, and diagnostic methods for patients with NMD.

## #791- Improving diagnostic rates for mitochondrial diseases using enhanced WGS analysis and RNA-seq

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**Introduction:** Despite recent improvements in genomic technologies and increased use of whole genome sequencing, many patients with suspected mitochondrial myopathies (MMs) remain without a diagnosis, precluding access to precision care.

**Objectives:** We sought to boost diagnostic rates by combining bespoke bioinformatic analysis, based on deep phenotyping and RNA sequencing for a subset of cases.

**Method:** After an initial semiautomated analysis of WGS data all undiagnosed cases were reviewed by a clinician to guide bespoke analysis and RNA-sequencing was undertaken in cases with tissue samples (muscle or fibroblasts) available, with analysis including manual inspection of Sashimi plots and DROP pipeline analysis.

**Results:** We included 102 WGS cases and 55 RNA-Seq analyses. By enhancing analysis and including RNA-Seq we were able to boost diagnostic rates from 16.6% to 39.2%. Analysis of new diagnoses shows a high proportion are not in mitochondrial genes, despite patients having respiratory chain enzyme and histological results supportive of an MM. Mitochondrial genes, and those MM mimic genes are best expressed in muscle and fibroblasts but not blood. The study has led to the identification of novel genetic causes of non-mitochondrial myopathy and neuropathy.

**Conclusions:** MM presentations are non-specific and even biochemical abnormalities and pathological changes e.g., COX negative fibres and ragged red fibres, can be secondary to non-mitochondrial disease. The overlap with a broad range of alternative diagnoses means one size does not fit all for these patients, and greater emphasis needs to be put on a clinician-led bespoke analysis of data, supplemented with RNA-Seq where possible.

#747- Introducing routine diagnostic Whole Genome Sequencing into the clinic

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**Introduction:** Recruitment to the 100,000 Genomes Project (100KGP) was completed in December 2018. This project has provided thousands of families with a genetic diagnosis, allowing development in all areas of genomic medicine. Since April 2022, whole genome sequencing (WGS) has been introduced as a diagnostic test in the UK National Health Service (NHS) for certain disease groups including Charcot-Marie-Tooth disease (CMT). However, in order to effectively use WGS, clinicians must overcome certain challenges in the clinical setting.

**Objectives:** To assess the introduction of routine WGS for inherited neuropathy panel testing in our peripheral nerve clinics with special reference to clinician understanding and patient consent.

**Methods:** We describe our experience of introducing routine diagnostic WGS into our Peripheral Neuropathy Clinics since April 2022.

**Results:** All clinicians (including six consultants) needed updated training in consent for WGS. This was achieved by online information being made available by the NHS diagnostic laboratory, by a virtual training seminar and through face-to-face training by a dedicated inherited neuropathy specialist nurse. All 6 consultants are now trained and comfortable obtaining consent for WGS. We have requested 88 WGS tests including 68 singleton, one duo and 19 trio. One patient declined testing and two patients agreed to WGS but declined participation in research.

**Conclusion:** Utilising WGS requires expert training for clinicians, particularly in the consent process with regards unexpected findings. Dedicated time in clinic is needed to achieve this and hence a specialist nurse or equivalent is essential for delivering this service safely and effectively.

#784- GENETIC AND EPIDEMIOLOGY CHARACTERIZATION OF A LARGE COHORT OF PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS: TEN YEARS OF EXPERIENCE IN A DEDICATED NEUROMUSCULAR CLINIC IN ITALY (The NEMO Clinical Center)

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**Introduction :** The extensive genetic and clinical characterization of patients with Amyotrophic lateral sclerosis (ALS) in the era of upcoming targeted trials is mandatory, due to the intrinsic heterogeneity of the disorder .

**Objectives:** to depict the genetic and epidemiologic characteristics of a cohort of ALS patients regularly followed at one single Italian neuromuscular center in the last 10 years.

**Methods:** 1729 ALS patients were screened for SOD1, FUS, TDP43, C9ORF72 genes.

**Results:** mutations were found in 188/1729 (10.8%), 61.5% fALS patients and in 9.5% sALS cases. Out of 188 mutated patients, 37 (19.6%) were SOD1, 111 (59%) C9orf72 and 26 (13.8%) TDP43 mutated. Among the 14 (7.4%) FUS mutated patients 3 had a juvenile onset ALS while 11 adult onset ALS. The mean age of symptoms onset and median tracheostomy free survival time were respectively 53.72 years+8.75 and 125.87 months among SOD1 mutated patients; 57.1y+8.7 and 42.2m among C9Orf72; 55.1y+11.84 and 54.5m among TDP43; 18.5y+10.4 and 45.6m among juvenile FUS and 54.3y+10.44 and 57.5m (8.3-90.4) among adult onset FUS. 63 mutated ALS patients are still alive and regularly followed up: 19 SOD1, 33 C9Orf72, 3 FUS, 8 TDP43.

**Conclusions:** Our data confirm the high incidence of the four most common gene mutations with the prevalence of C9orf72 expansions. The clinico-genetic correlation is fundamental in order to define disease trajectory and better finalized tailored therapeutic intervention. Thus, we are developing a predictive model to combine genetic outputs and extensive clinical evaluations in order to implement the knowledge on ALS natural history.

#785- Magnetic resonance imaging and spectroscopy biomarkers for primary mitochondrial myopathies: preliminary results of a longitudinal study

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**Introduction:** Primary mitochondrial myopathies (PMM) are genetic disorders with defects of the oxidative phosphorylation affecting predominantly the skeletal muscles. Currently, there are no disease modifying therapies for PMM. One major difficulty to clinical trials in PMM is the lack of reliable and reproducible biomarker that can catch the disease severity and progression.

**Objectives:** This is the first study aiming to examine the validity of MRI quantified muscle volume, fat fraction, and 31 phosphorous magnetic resonance spectroscopy (31P-MRS) of thigh muscles before, during, and after exercise as outcome measures with a direct correlation of clinical and functional measures used in PMM.

**Methods:** This is a prospective observational cohort study of patients with genetically confirmed PMM. Age and sex-matched healthy subjects (HS) are also recruited. Assessments are done at baseline and 12 months. Correlations between MRI outcomes and clinically relevant outcome measures are performed.

**Results:** Only baseline results are reported. Twenty adults with PMM (10 m.3243A>G and 10 single deletion of mitochondrial DNA) were recruited, 6 females and 5 males in each group, mean ages of 51.2±9.3 and 48.2±14.4 years, respectively. They were matched with 10 HS, with mean age of 47.9±14.3 years. All patients had fatigue. A direct correlation between age and fat fraction in thigh muscles in PMM patients was present. Muscle strength was reduced in those with increased fat fraction. The vastus lateralis 31P-MRS showed a more profound normalised phosphocreatine signal reduction during knee extension exercise, and a slower recovery time compared to HC.

**Conclusions:** MRI and 31P-MRS might be valuable biomarkers in clinical trials.

#775- The Inclusion Body Myositis Health-Index (IBM-HI): Development of a Novel, Disease Specific Patient-Reported Outcome Measure for IBM in Clinical Trials

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**Introduction:** This study outlines the development and validation of a new, multifactorial patient-reported outcome (PRO) tool called the Inclusion Body Myositis-Health Index (IBM-HI).

**Objective:** To create a fully validated, disease-specific PRO for IBM that is capable of detecting clinically relevant changes in disease burden over time and satisfying FDA criteria for use in therapeutic trials and labeling claims.

**Methods:** We conducted qualitative interviews with individuals with IBM to identify potential symptoms of importance and used a cross-sectional study to determine the prevalence and impact of these symptoms. We selected symptom questions for IBM-HI based on their frequency and importance to study sample as well as their potential to respond to therapeutic intervention. Using factor analysis, we grouped questions into subscales. We performed beta testing, test-retest reliability assessments, and known groups analysis to optimize the clarity, usability, meaningfulness, responsiveness, reliability, and differential ability of the IBM-HI.

**Results:** Ten individuals with IBM participated in initial interviews; 569 participants completed the cross-sectional study and known group's analysis; 15 participants completed beta testing; and 20 participants completed reliability evaluations. The Final IBM-HI measures a patient's perception of their multifactorial disease burden using 13 subscales. Average time of completion of IBM-HI was 11 minutes and reported that it was easy to complete. Validation testing showed the IBM-HI to be relevant, understandable, and reliable. IBM-HI total and subscale scores effectively distinguished between individuals with differing levels of disease severity.

**Conclusions:** IBM-HI is a fully validated PRO, ready for use in IBM clinical trials and patient monitoring.

#807- Investigation into the Long-Term Prognosis of Patients with Sporadic Inclusion Body Myositis

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**Information and Objectives:** Sporadic inclusion body myositis (IBM) is the most common inflammatory myopathy in individuals over the age of 50. IBM is slowly progressive and leads to pronounced weakness in finger flexors, knee and ankle extensors, impairing the patient's abilities to perform activities of daily living in advanced stages. Often, patients initially seek care with a myositis specialist, but are lost to follow-up when ambulation becomes difficult, limiting our knowledge on late-stage IBM.

**Methods:** Patients enrolled in the Johns Hopkins Myositis Research Registry between 2003-2018 with a confirmed diagnosis of IBM were contacted via phone and invited to participate in a 40-minute phone interview conducted via standardized questionnaire. The questionnaire assessed the presence of other autoimmune conditions, the severity of common IBM symptoms, exercise habits, past hospitalizations and current living arrangements and contained validated scales such as the IBMFRS, PGIS and PGIC.

**Results:** A total of 103 interviews were conducted with IBM patients. The mean age of the cohort was 72 years, ranging from 48 to 87 years. The mean time elapsed since onset of symptoms was 15.5 years, ranging from 3 to 35 years, and two thirds (67%) of the interviewed patients were male, and 85% were white, and about 10% African American.

**Conclusions:** Data analysis for this project has just started and will be conducted over this summer in an attempt to identify factors that will predict long-term prognosis in IBM.



#777- Rasch Analysis of the Patient-Reported Outcomes Measurement Information System (PROMIS) Parent Proxy (PP) Upper Extremity (UE) Item Bank Administered to Caregivers of Patients With Duchenne Muscular Dystrophy at Nationwide Children's Hospital

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**Introduction:** There is growing emphasis on health-related quality of life (HRQoL) as an important outcome in rare diseases. Central to assessing HRQoL are patient-reported outcome (PRO) measures that evaluate aspects of the disease and treatment meaningful to patients. The “patient voice” has been challenging to incorporate in practice because generic PROs frequently fail to reliably quantify changes important to individuals with rare diseases.

**Objective:** To describe the process for evaluating utility of PROs in a rare disease and identify modifications that improve the responsiveness of the instrument in the target population. We explored psychometric properties of the generic PROMIS PP UE v1.0 (29 items) through Rasch analysis for suitability of use in DMD.

**Methods:** Caregivers of patients with DMD  $\geq 8$  years of age at Nationwide Children's completed PROMIS PP UE (N=206). Rasch analysis assessed the internal functioning of items and scores. Statistics yielded from this analysis provided detailed measurement and diagnostic information to identify problematic items and improve the scale's performance.

**Results:** The final Rasch model included 21 items, with response options regrouped when necessary. Customized PROMIS PP UE satisfied all Rasch model assumptions, with a nonsignificant item-trait interaction ( $P=0.095$ ). The scale's power to discriminate among respondents with different levels of UE function was very satisfactory (Person Separation Index = 0.947). This process could be used by other researchers to improve the sensitivity of PROs for their field of interest.

**Conclusion:** This is the first study that assessed psychometric properties of PROMIS PP UE in DMD.

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**Disclosures:** **IA, SP:** Employees of Sarepta Therapeutics, Inc., and may hold stock/options in the company. **CL:** Independent biostatistician who received funding from Sarepta Therapeutics, Inc., to help with the analysis. **TC:** Employee of F. Hoffmann-La Roche Ltd. **LA, NR, MI, LL:** Employees of the Nationwide Children's Hospital and have provided the data for this study. Nationwide Children's Hospital receives grant funding for other research initiatives from Sarepta Therapeutics, Inc.

#778 Comparison of Functional Ability Between 4–7 Years of Age (YOA) Children With Duchenne Muscular Dystrophy (DMD) to that of Typically Developing Age-Matched Children Using the Patient-Reported Outcomes Measurement Information System (PROMIS) Parent Proxy (PP) Mobility and Upper Extremity (UE) Questionnaires

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**Introduction:** DMD is a rare, progressive neuromuscular disorder characterized by diminishing functional ability. PROMIS are generic patient-reported outcomes quantifying the impact of disease on physical, social, or cognitive function. PROMIS PP Mobility and UE questionnaires are administered in DMD studies. Comparison with typically developing children allows for a comprehensive view of disease severity and exploration of scale responsiveness in a population of interest.

**Objective:** To compare PROMIS PP Mobility and UE questionnaires administered to boys with DMD versus typically developing children, both 4–7 YOA.

**Methods:** Nationwide Children’s recruited caregivers of DMD and typically developing children (both 4–7 YOA) to complete PROMIS PP Mobility (v1.0) (n=73, n=182, respectively) and UE (v1.0) (n=73, n=176, respectively) questionnaires. Total raw and T-scores were calculated.

**Results:** Boys with DMD scored numerically lower than typically developing age-matched peers. The difference in scores between boys with DMD and typically developing children became greater at older ages. Specifically, the ability to perform functions such as “walk more than one block,” “walk upstairs without holding on,” “carry books in backpack,” “open rings in a school binder,” “take a bath,” and “pour drink from full pitcher” became increasingly harder to complete for DMD boys.

**Conclusion:** From early childhood, boys with DMD perform worse than typically developing peers in terms of physical abilities. Pattern of differences indicates deterioration in lower and upper body function, consistent with DMD disease, which demonstrates that PROMIS PP Mobility and UE questionnaires can capture change in physical function in DMD boys 4–7 YOA.

**Sponsorship:** The publication was funded by Sarepta Therapeutics, Inc.

**Disclosures:** **SP, IA:** Employees of Sarepta Therapeutics, Inc., and may hold stock/options in the company. **CL:** Independent biostatistician who received funding from Sarepta Therapeutics, Inc., to help with the analysis. **TC:** Employee of F. Hoffmann-La Roche Ltd. **LA, NR, MI, LL:** Employees of the Nationwide Children’s Hospital and have provided the data for this study. Nationwide Children’s Hospital receives grant funding for other research initiatives from Sarepta Therapeutics, Inc.

#788- Pre- and post-natal outcomes in congenital and childhood onset DM1 - the impact of parental diagnostic delay

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**Introduction:** Myotonic dystrophy type 1 (DM1) is often diagnosed during pregnancy in women or after the development of symptoms in one parent. This reflects in missed prenatal diagnosis. However, the impact of the parental diagnostic delay on the prognosis of their children is not established.

**Objectives:** To describe the perinatal characteristics and the developmental outcomes of patients with congenital (CDM) and childhood (ChDM) DM1 in relation to the timing of diagnosis of the affected parent.

**Methods:** Retrospective study of patients with CDM and ChDM followed by 13 Italian centres. Children's disease type and parental timing of diagnosis were recorded. CTG expansions were classified as E1=<500, E2=500-1.000, E3=1.000-1.500, E4>1.500. Perinatal features, motor and cognitive development were collected.

**Results:** Seventy-one children were included, 41 CDM, mean( $\pm$ SD) age 12.0 $\pm$ 5.1y, 30 ChDM mean age 12.7 $\pm$ 4.8y. All CDM had maternal inheritance. Only 6/41 were tested antenatally given the known maternal diagnosis; 2/41 children born to known affected mothers were only diagnosed at birth.

Perinatal information was available for 21 children; 4 were born preterm, 15/21 required NICU >48 hours, 16/19 had ambulation and 14/18 speech delay. 2/21 had normal QI.

Of the 30 ChDM, 17 had paternal inheritance. 6/30 were diagnosed in-utero given the known parental diagnosis. Perinatal information was available in 19 children. All were born at term, one required NICU. 1/19 had ambulation and 4/19 speech delay. Only 7/13 had normal QI.

**Conclusions:** Diagnostic delay in DM1 is well-described but when this occurs in child-bearing age the impact on the pre- and perinatal outcome of the affected children is high.

## #673- MR Neurography and Quantitative Muscle MRI of Parsonage Turner Syndrome Involving the Long Thoracic Nerve

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**Introduction:** Parsonage-Turner Syndrome (PTS) is characterized by severe, acute upper extremity pain and subsequent paresis and most commonly involves the long thoracic nerve (LTN). MR neurography (MRN) can detect LTN hourglass-like constrictions (HGCs) and quantitative muscle MRI (qMRI) can quantify serratus anterior muscle (SAM) neurogenic changes.

**Objective:** 1) To characterize MRN/qMRI findings in LTN-involved PTS. 2) To investigate associations between qMRI biomarkers and EMG motor unit recruitment (MUR) levels.

**Methods:** We retrospectively investigated 30 PTS subjects (25M/5F, mean/range age=39/15-67 years) with scapular winging who underwent 3.0 Tesla bilateral chest wall qMRI and unilateral brachial plexus MRN. EMG was performed on average 185 days from symptom onset (all  $\geq$ two weeks from symptom onset) and 5 days preceding MRI.

**Results:** The LTN was identified on MRN in 23/30 patients and HGCs were seen in 91% of cases (21/23). All 30 subjects had diffuse SAM edema on the affected side compatible with active denervation. Additionally, qMRI was significantly different to the contralateral, uninvolved side: increased T2 ( $p < 0.001$ ) and fat fraction ( $p = 0.013$ ), and decreased muscle diameter ( $p = 0.003$ ) and cross-sectional area ( $p < 0.001$ ). There were no significant associations between individual qMRI biomarkers and EMG MUR levels.

**Conclusion:** MRN can confirm PTS by identifying HGCs in most cases of LTN involvement. qMRI provides an objective measure of SAM changes. Lack of association between qMRI and EMG MUR levels for the SAM, as has been previously reported for other denervated muscles, could be related to MRI breathing artifacts and EMG sampling error. Further investigation and analysis are warranted.

## #733-Not just liver enzymes: Transaminitis as a marker of Immune Mediated Necrotizing Myopathy

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**Introduction:** Immune mediated necrotizing myopathy (IMNM) is an autoimmune disease affecting skeletal muscles resulting in elevated markers of muscle injury including CK, AST and ALT. For patients who present with transaminitis, IMNM diagnosis can be delayed by extensive evaluation for liver pathology.

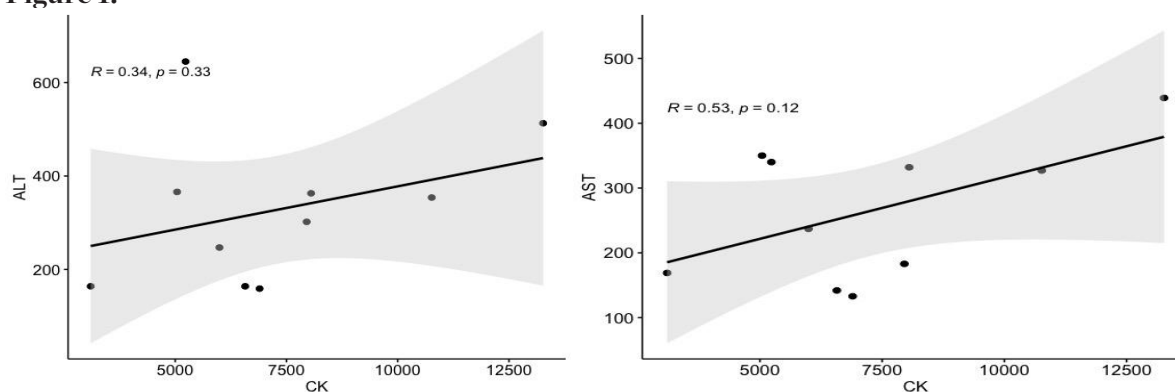
**Objectives:** Investigate levels of AST and ALT and their correlation with CK in IMNM.

**Methods:** A retrospective review of patients evaluated at UNC with a new diagnosis of IMNM was completed. Values for CK, AST and ALT at the time of diagnosis were extracted. Group mean and standard deviations were calculated and Pearson correlations were calculated between CK and transaminase levels.

**Results:** 10 patients were identified (4 female). Mean age at time of diagnosis was 68.7 years (SD 10 y). All patients had elevated CK (mean 7288 U/L, SD 2943 U/L), AST and ALT levels (AST mean 265 U/L, SD 105 U/L; ALT mean 327 U/L, SD 159 U/L) at initial presentation. There was a positive correlation trend between CK and AST ( $r = 0.53, p = 0.12$ ) and ALT ( $r = 0.34, p = 0.33$ ) (Figure 1). AST/ALT ratio was 0.8.

**Conclusions:** We demonstrated that transaminases in patients with initial diagnosis of IMNM can be elevated more than 5 times the upper limit of normal and show higher levels of ALT compared to AST; both parameters typically considered to be markers of primary liver disease. These findings can potentially impact existing protocols for evaluation of patients with elevated transaminases and expedite diagnosis for patients with IMNM.

**Figure 1:**



Pearson correlations between CK and AS and ALT levels in patient with IMNM.

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## Mechanism of Disease and Less Common Disease Presentations

### #810- Nematodes deficient in TANGO2 homologs exhibit strong neuromuscular phenotype suggestive of bioenergetic dysfunction

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**Introduction:** Rhabdomyolysis occurs through a convergent pathway involving sarcolemmal calcium influx and protease activation; however, how defects in several rhabdomyolysis-associated genes upstream of this pathway cause myocyte dysfunction remains unknown. TANGO2-deficiency disorder (TDD) is a poorly-understood autosomal recessive condition associated with a multitude of symptoms including rhabdomyolysis in the setting of metabolic crisis. Adult patients with TDD have been recently reported to have substantial limb-girdle weakness.

**Objectives:** Our overall aim is to elucidate the function of TANGO2 protein using *C. elegans* as a model system. In this study, we characterized the phenotype of nematodes deficient in *hrg-9* and *hrg-10*, two homologs of TANGO2.

**Methods:** Double knockout worms (*hrg-9*<sup>-/-</sup>/*hrg-10*<sup>-/-</sup>) were generated using CRISPR-Cas9 genome editing techniques. We assessed 1) exercise tolerance by counting the number of swimming worms after 20 minutes in an isotonic buffer solution; 2) brood size, and 3) intestinal fluorescence following exposure to a fluorescent substrate, as a proxy for eating behavior.

**Results:** *hrg-9*<sup>-/-</sup>/*hrg-10*<sup>-/-</sup> worms exhibited markedly reduced exercise tolerance ( $X^2=22.53$ ;  $p<0.0001$ ) and brood size ( $\bar{x}=112\pm 28.2$ ) compared to wildtype controls ( $40.8\pm 20.9$ ;  $t=6.0$ ;  $p<0.0001$ ). They also exhibited lower intestinal fluorescent intensity ( $t=2.8$ ;  $p=0.0067$ ) suggestive of reduced ingestion.

**Conclusions:** Nematodes deficient in TANGO2 homologs exhibit a strong phenotype reminiscent of other *C. elegans* strains with known bioenergetic dysfunction. These findings are in line with other work implicating TANGO2 as a potential regulator of lipid homeostasis and mitochondrial beta-oxidation and support additional studies focused on the localization and function of TANGO2 homologs in *C. elegans* body wall muscle.



## #766- Amyotrophic Lateral Sclerosis and Spinocerebellar Ataxia Type 2: A Familial Case Report

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Spinocerebellar Ataxia Type-2 (SCA2) and Amyotrophic Lateral Sclerosis (ALS) are genetically linked through a trinucleotide (CAG) repeat expansion in the ATXN2 gene. The length of CAG repeat expansion in the ATXN2 gene is directly related to age of onset and severity of SCA2. There is also evidence to suggest that CAG repeat length correlates with expected phenotype (ALS vs. SCA2). There are few reports demonstrating intrafamilial phenotypic variability of ATXN2 mutations. Here we report a family with separate and distinct phenotypes via repeat expansions in ATXN2, whose presentations do not align with their expected phenotypes based on CAG repeat size. A patient, diagnosed with ALS at 36-year-old, exhibited painless bilateral arm weakness, dysarthria, and progressive motor impairment leading to quadriplegia and respiratory failure. Her brother was diagnosed with SCA2 at 16-year-old, presenting with falls, dysarthria, and ataxic features. The family history included olivopontocerebellar degeneration, suspected SCA, and possible ALS.

This case documents a patient who was diagnosed with ALS without manifested signs of SCA2 despite having full CAG repeat expansion 40/23. Despite attempts to characterize a distinction between disease entities by mutation history, this case highlights heterogeneity in the genetic background and development of ALS versus SCA2.

This case highlights the need for a deeper understanding of the complex relationship between ATXN2 mutations and disease presentation. Clinicians, genetic counselors, and researchers should consider the potential variations in disease expression based on repeat. This knowledge has important implications for appropriate genetic testing, accurate risk assessment for family members, and access to targeted therapies.



#786- Characterization of TDP-43 cryptic splicing

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TDP-43 is an RNA-binding protein with a prominent role in mRNA splicing, that mislocalises and forms aggregates in the cytoplasm in neurodegenerative disorders affecting both brain and muscle. The concomitant loss from the nuclei leads to the inclusion of non-conserved cryptic exons (CEs), which often contain premature stop codons or induce frameshift, causing degradation of the CE-containing transcripts through nonsense-mediated decay (NMD).

The aim of this work is to characterise CEs, their sensitivity to differential TDP-43 loss of function and to NMD, and their tissue-specificity.

Thus, we gathered previously published data and generated cell lines as models for TDP-43 loss of function, and performed RNA-sequencing on them.

First, we analysed the impact of increasing levels of TDP-43 knockdown, discovering patterns of response and maximal expression for different CEs. Later, we inhibited NMD both with cycloheximide and through the knockdown of the key NMD factor UPF1, showing that some CEs are spared from NMD and therefore have the potential to be translated and used as biomarkers. Moreover, we found CEs that are masked by NMD, and orthogonally validated them through qPCR, proteomics, and post-mortem RNA-sequencing data. Finally, we report on the ongoing effort to assess TDP-43 cryptic splicing and impaired RNA processing in muscle tissue and diseases.

Overall, this study expands our knowledge of the TDP-43 CE biology and provides evidence for novel biomarkers and therapeutic targets in TDP-43 proteinopathies.

## #763- Evaluation of the Role of Glial Factors in the Pathogenesis of Spinal Muscular Atrophy

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**Introduction:** Diagnostic and therapeutic biomarker studies for spinal muscular atrophy (SMA) patients have gained momentum after novel disease modifying treatments. There are growing evidence that the glial cells and related neuroinflammation play role in SMA-related neurodegeneration.

**Objectives:** To investigate the role of glial factors in the pathogenesis of SMA.

**Methods:** Cerebrospinal fluid (CSF) levels of glial-derived neurotrophic factor (GDNF) and glial fibrillar acidic protein (GFAP) were measured by ELISA in treatment-naive SMA adult patients. CSF of patients undergone lumbar puncture with the suspicion of pseudotumor cerebri (PTC) were used as control.

**Results:** Twenty-two SMA patients and ten PTC patients were analyzed. GFAP levels were higher in SMA group compared to controls ( $p < 0.05$ ), while GDNF levels were found to be significantly lower ( $p < 0.05$ ) in SMA group.

**Conclusions:** This study supports the hypothesis that glial cells play a role in the pathogenesis of SMA. Considering the studies in literature, lower levels of GDNF in this study may highlight its biologically active role in the pathogenesis of SMA. Lower levels of GDNF accompanying with elevated levels of GFAP may be used as a diagnostic biomarker for SMA.

## #762- Proteomic characterisation of molecular pathways involved in Type III Spinal Muscular Atrophy

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**Introduction:** Spinal muscular atrophy (SMA) is classified into four clinical sub-types, from Type I (severe), to Type IV (adult-onset). There is no cure for SMA, but gene-based treatment options have recently become available. Almost all pre-clinical work, however, has focused on identification and characterisation of molecular pathways associated with severe SMA.

**Objectives:** To determine whether similar molecular pathways are involved in Type III SMA compared to those detected in Type I and II SMA.

**Methods:** Using quantitative proteomics analysis, protein extracts from fibroblasts, myoblasts and induced pluripotent stem (iPS) cell-derived motor neurons from SMA Type III patients were compared with age-matched controls. Datasets were interrogated to identify commonalities between them and were then compared to datasets generated from SMA Type I and II fibroblasts and iPS cells using bioinformatics analysis.

**Results:** Dysregulated proteins were identified in the SMA Type III fibroblasts (n=77), iPS-derived motor neurons (n=71) and myoblasts (n=363) compared to control cells, but only one protein was consistently dysregulated in all three cell types from SMA Type III patients. Bioinformatics analysis indicated that some cellular and molecular pathways in Type II and III SMA were a protraction of that seen in Type I SMA, but strongly suggested that different SMA severities are associated with distinct molecular processes.

**Conclusions:** This work highlights new avenues for future work aimed at developing severity-specific therapies for SMA. Future work will also focus on validating the protein consistently dysregulated across the SMA Type III cells as a potential biomarker for Type III SMA.

#724- Atypical presentation of chronic inflammatory demyelinating polyneuropathy

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**Introduction:** We present a unique acute onset chronic inflammatory demyelinating polyneuropathy (CIDP) with multiple cranial nerves and bulbar involvement.

**Case Presentation:** 28-year-old woman presented to our hospital with 14-day history of numbness and tingling, impaired coordination, hoarseness and areflexia 3 weeks after a viral infection. MRI lumbar and lumbar puncture were consistent with acute inflammatory demyelinating polyneuropathy (AIDP) and she was treated with intravenous immune globulin (IVIg) and discharged with moderate improvement in her symptoms. She returned 2 weeks later with worsening of neck and proximal muscles weakness and bilateral facial nerve and vocal cord paralysis. She received five sessions of plasma exchange (PLEX) for possible recurrent AIDP and discharged with significant improvement of her symptoms. She returned to the hospital after a week with mild to moderate dysarthria, mild anisocoria, reduced sensation to pinprick in the right V3 distribution and tongue weakness in addition to worsening of prior symptoms. The patient admitted with CIDP diagnosis and received PLEX. Work ups looking for diseases mimicking CIDP were negative. Electrodiagnostic study revealed a chronic, inactive, demyelinating, motor>sensory polyneuropathy affecting upper>lower extremities. The patient was placed on PLEX, prednisone and CellCept with significant improvement of her symptoms.

**Conclusion:** CIDP typically does not present acute onset and multiple cranial nerves involvement and bulbar symptoms are very rare. The findings in this case report may prompt further understanding of clinical and imaging characteristics associated with acute onset CIDP and care measures that could help identifying patients at risk of severe course of the disease.

#760- Critical illness polyneuropathy/myopathy are associated with exposure to respiratory illness during critical care stays

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**Introduction:** Critical illness polyneuropathy and myopathy (CIP/CIM) are debilitating complications that may follow intensive/critical care (ICU) hospitalizations. Known risk factors include ventilator use, multiple organ failure, hyperglycemia, neuromuscular blockade, and potentially respiratory illnesses such as COVID-19.

**Objectives:** Examine associations between ICU-concurrent respiratory illnesses and CIP/CIM.

**Methods:** Propensity score matching (1:1) utilizing TriNetX integrated analytics controlled for known CIP/CIM risk factors in data from 80 healthcare organizations (100.8M adults). Odds ratios (OR) with 95% confidence intervals (CI) for a CIP and/or CIM diagnosis within 3 months of an ICU-concurrent respiratory illness were calculated.

**Results:** For CIP and/or CIM, the OR for any ICU-concurrent respiratory illness (N=937,162) was 19.5 (95% CI 16.4, 23.2). ORs were 6.91 (6.10, 7.82) for COVID-19 (N=251,298), 2.91 (2.65, 3.18) for influenza (N=254,096), and 3.05 (2.78, 3.34) for pneumonia (N=251,652). For exposure comparisons ORs were 1.60 (1.47, 1.74) for COVID-19 versus influenza (N=181,074), 1.57 (1.44, 1.71) for COVID-19 versus pneumonia (N=178,494), and 0.991 (0.918, 1.07) for influenza versus pneumonia (N=253,524).

**Conclusion:** CIP/CIM diagnoses are associated with elevated odds of exposure to respiratory illnesses, particularly COVID-19, during ICU hospitalizations. The cause of CIP/CIM remains unknown, but improving treatments for respiratory illnesses and optimizing recognized interventions such as early rehabilitation and glycemic control may reduce occurrence.

## #720- Review of Acute Rhabdomyolysis in Genetic Disorders vs Unaccustomed Exercise

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**Aims:** The aim of this study was to identify whether presenting features of patients presenting with AR due to unaccustomed exercise (UE) can be distinguished from those presenting with metabolic myopathies.

**Methods/Materials:** We retrospectively reviewed case notes of 51 patients presenting with AR between January 2020 and December 2022. A questionnaire was sent to patients to complete. The study was approved by our hospital internal review board.

**Results:** Of 51 patients included in this study 19 (37%) were diagnosed with AR due to UE, 10 (20%) with GSDV, 10 (20%) with CPT-2 deficiency and 12 (23%) with RYR-1-related AR. Investigation included testing on a panel of 65 genes associated with AR or targeted single gene testing. The mean age was 37 years (19-75); 84% were males. Median serum CK during AR episodes was 55 000iu/L (8 000-300000 iu/L). GSDV patients had highest baseline CK (mean CK:1980) ( $p=0.05$ ). 30 patients (59%) were admitted hospital of whom 7 (14%) went to ITU and 6 (12%) required renal dialysis. None of these were UE patients... ITU admission/ renal dialysis were most likely in CPT-2 deficiency ( $p=0.014$ ,  $p=0.049$ ). Triggers for AR were exercise, heat, fasting, fever and coffee. Neck muscle involvement occurred in CPT-2 deficiency ( $p=0.05$ ). Onset of AR was within minutes of exercising GSDV, after 2-36 hours in CPT-2 & RYR-1, where and more than 36 hours after exercise in UE ( $p<0,001$ ).

**Conclusion:** Timing of onset of AR can help to differentiate specific underlying metabolic disorders from UE. This may be useful in guiding diagnostic investigations.

## #814- Late-onset autophagic vacuolar myopathy with sarcolemmal features

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**Introduction:** Autophagic vacuolar myopathies with sarcolemmal features (AVSF) include Danon disease, X-linked myopathy with excessive autophagy (X-MEA), X-linked congenital autophagic vacuolar myopathy, infantile autophagic vacuolar myopathy, and adult-onset autophagic vacuolar myopathy with multiorgan involvement.

**Case Report:** A 63-year-old man with history of diabetes and intestinal metaplasia presented an eight-year history of severe, progressive and generalized myalgias. There was no family history or consanguinity, history of toxic exposure or infection.

**Methods and Results:** Exam did not reveal muscle weakness although it was limited by pain, there was no muscle atrophy or myotonia, and deep tendon reflexes were normal. Creatine kinase (800IU/L), aldolase, ESR and CRP were elevated. Antinuclear antibodies, rheumatoid factor, PM1/Scl and PI-7 antibodies were elevated. Electromyogram revealed an irritable myopathy. Two muscle biopsies with an eight-year interval were concerning for progression of an autophagic vacuolar myopathy with complement deposition in sarcolemma of non-necrotic muscle fibers. A two-phase whole body bone scan (99mTc-HDP) showed increased tracer uptake in muscles of upper and lower extremities. Whole body PET did not show any malignancy. Cardiac evaluation revealed a non-obstructive hypertrophic cardiomyopathy. Neuromuscular Comprehensive genetic panel did not identify mutations in *GAA*, *LAMP2* or *VMA2I* but a pathogenic variant in *RYR1* gene (c.6640 G>A, p.Val2214Ile) and a VUS in *SLC16A1* (c.10G>A, p.Ala4Thr). Steroids and IVIG infusions did not provide benefit. Whole genome sequencing (WGS) was performed (pending).

**Conclusions:** Myalgias may be the main symptom of AVSF. Unless WGS reveals another cause, we wonder whether this clinico-pathological phenotype is a manifestation of *RYR1*-related myopathy.

#743- Hemodynamic response to exercise and mechanisms of exercise intolerance in patients with Myositis

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**Introduction:** Exercise intolerance is a common symptom in patients with inflammatory myopathies (IIMs), yet the hemodynamic response to exercise and the mechanisms contributing to intolerance remain unclear.

**Objective:** To characterize the hemodynamic response to exercise and confirm the specific mechanisms of impaired oxygen transport/utilization using both whole body (cardiopulmonary exercise testing [CPET]) and isolated single-knee extension (IKE) exercise in patients with IIMs.

**Methods:** 5 patients (3M including DM/IMNM/IBM) with IIMs (52±13 yrs, 33.5±8.3 kg/m<sup>2</sup>) and 9 (3M) controls (CON; 68±8 yrs, 25±3 kg/m<sup>2</sup>) underwent CPET to determine peak oxygen uptake ( $\dot{V}O_2$ ; indirect calorimetry), cardiac output (Qc; acetylene rebreath), and arterial-venous O<sub>2</sub> difference ( $\Delta a-vO_2$ ). Leg blood flow (LBF; ultrasound) was measured during IKE at 5, 10, and 15 Watts (W). In IIMs, blood was collected from the common femoral vein of the exercising leg to calculate leg  $\dot{V}O_2$  ( $L\dot{V}O_2$ ; LBF x  $\Delta a-vO_2$ ). Data were compared between-groups via t-tests and within-groups via repeated-measures ANOVA.

**Results:** Peak  $\dot{V}O_2$  was not different between IIMs and CON ( $P=0.124$ ), but peak Qc ( $P=0.042$ ) was elevated and  $\Delta a-vO_2$  ( $P=0.019$ ) was diminished in IIMs; the Qc- $\dot{V}O_2$  slope was higher in IIMs (7.2±1.6 vs 5.8±1.1 L/min/L/min,  $P=0.080$ ). During IKE, LBF (both,  $P<0.001$ ) increased from rest to 5W, but only increased thereafter in CON ( $\Delta 595.2\pm 385.5$  ml/min,  $P=0.011$ ; IIMs:  $\Delta 129.6\pm 221.4$  ml/min,  $P=0.976$ ), likely because IIMs failed to increase in  $L\dot{V}O_2$  from 5-15W ( $\Delta 13.87\pm 29.8$  ml/min  $P=0.869$ ).

**Conclusion:** Despite similar  $\dot{V}O_2$ , IIMs showed a hyperdynamic circulatory response to exercise and impaired muscle oxygen diffusion and/or mitochondrial capacity that limits oxygen transport and utilization.



## #709- Myasthenic Syndrome Due to Tubular Aggregate Myopathy: A Case Report

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**Introduction/Background:** Tubular aggregate myopathies are a rare group of disorders with characteristic accumulation of densely packed tubules in skeletal muscle fibers. As a descriptive pathologic diagnosis, it includes a heterogeneous array of phenotypic presentations including exertional myalgia, muscle cramping and stiffness, progressive proximal weakness, fatigability, as well as periodic paralysis.

**Case Report:** A 55 year old woman presented with 2 to 3 years of generalized fatigable weakness. Over the course of a year, she developed progressive decline in respiratory function from 90% to 42% upright forced vital capacity. Initial EMG showed only mild polyphasia; repeat EMG showed nonirritable myopathy. Genetic testing showed heterozygous variants of uncertain significance in ACADM, CAPN3, COLG6A2, GFER, GOSR2, PLEC, and SMN1/SMN2. A right biceps muscle biopsy showed a tubular aggregate myopathy. Notably, genes known to be associated with tubular aggregate myopathy were negative, including CASQ1, STIM1, RYR1, ORAI1. Empiric use of pyridostigmine enabled the patient to walk for longer distances, though repetitive nerve stimulation and single fiber EMG were both negative for neuromuscular junction abnormalities.

**Conclusion:** 1) muscle biopsy should be considered in atypical cases of myasthenic syndromes, 2) symptomatic improvement with pyridostigmine is not specific for or diagnostic of myasthenia gravis, and 3) tubular aggregate myopathies are rare, and as a descriptive pathological diagnosis, consist of a heterogenous group of phenotypes. Negative genetic testing for known genetic causes of tubular aggregate myopathy does not exclude the diagnosis.

#666- Late onset CMT2A can be a diagnostic challenge when presenting with vague sensory symptoms

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**Introduction:** Mutations in the Mitofusion 2 gene have been reported to cause CMT2A. Mitofusion 2 is a protein that is important in mitochondrial fusion. It is well known that CMT2A can have both early onset more severe phenotypes and late onset milder phenotypes. This abstract investigates the clinical features of the late onset subset.

**Methods:** 4 subjects were evaluated using clinical, laboratory, electrophysiological and genetic data .

**Results:** All four subjects had a challenge to get to a diagnosis given the vague sensory nature of their presentation. One presented with sharp pains in his hands, confused for carpal tunnel syndrome. Another had a sunburn sensation in her legs and the last two had diffuse whole body parestheias which were all attributed to possible psychogenic causes. Two out of the four electrodiagnostic testing resulted in borderline abnormalities, which could be considered within normal limits including very mild delayed latencies in the sural and peroneal nerves. After extensive evaluations for all subjects, an MFN2 mutation was found and simple interventions such as gabapentin, alpha lipoic acid and Cymbalta helped control the symptoms. Genetic testing results revealed the following: subject 1, pathogenic deletion of exons 7-8, MFN2 c.749G>A reported as a suspected mutation, 881G>A variant of uncertain significance and C2119C> T pathogenic mutation.

**Conclusion:** Late onset MFN2 mutations can present with mild vague sensory complaints that can be a diagnostic challenge, but can be treated if recognized.

## #730- A stable human Schwann cell model of Charcot-Marie-Tooth disease type 1A

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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. Therapy development is hindered by limited insights into the molecular pathways involved in PMP22 accumulation and clearance and by limitations of current disease models.

**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 from healthy sural nerve were stably transfected with PMP22 and a promiscuous biotin ligase (BioID2) tag for labelling and identification of proteins in close proximity of PMP22 using mass spectrometry.

**Results:** Indicative of the myelinating Schwann cell dysfunction in CMT1A, transfectants overexpressing PMP22 had a spiky irregular morphology with intracellular, asymmetric aggregates of PMP22, which was not evident in control transfectants. Several hundred proteins in proximity of PMP22 were identified from BioID2 pulldowns which were associated with enriched molecular pathways including regulation of Schwann cell expansion, survival, and myelination. Close association between PMP22 and the endoplasmic reticulum membrane was evident, likely reflecting processing of the overexpressed protein.

**Conclusion:** 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.

#736- Defining paretic neuromuscular pathophysiology in a mouse model of spinal cord injury

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Columbia, MO, USA – <sup>5</sup>University of Missouri System NextGen Precision Health Initiative.

**Introduction:** The neuromuscular system demonstrates remarkable plasticity in response to changes in activity level, injury, and aging. Maladaptive remodeling of the motor unit (MU) or neuromuscular junction (NMJ) after injury may exacerbate disability and hinder recovery. Prior clinical/preclinical studies indicate substantial MU alterations in paretic muscle following stroke. Here, we investigated whether similar changes occur after spinal cord injury (SCI).

**Objective:** Characterize paretic neuromuscular pathophysiology in a mouse model of SCI, using in vivo longitudinal assessments and histological analyses.

**Methods:** Muscle physiology and MU electrophysiology were assessed weekly in SCI (T9 Transection) or control (Sham) mice, caudal to injury. Five weeks post-injury (wpi), NMJ transmission was evaluated using single-fiber electromyography (SFEMG), and tissue was collected to examine lumbar motoneurons and hindlimb NMJs.

**Results:** After SCI, paretic muscle weight markedly decreased, and tetanic contractility was reduced by ~45%. Electrophysiology indicated rapid, sustained MU loss. SFEMG revealed no difference in NMJ transmission at 5wpi. Though number of axonal inputs per NMJ was unchanged, NMJ size and colocalization of pre- and postsynaptic structures were reduced.

**Conclusions:** Similar to stroke, SCI prompts loss of functional MUs and contractility in paretic muscle caudal to injury. Findings of smaller NMJs with less pre-/postsynaptic overlap suggest reduced innervation. Forthcoming quantification of motoneuron size and counts will inform whether neuronal loss is occurring. Future studies will map evolution of NMJ morphology following SCI, assess synaptic transmission at earlier timepoints, and explore physiological silencing of MUs as an alternative explanation for the observed functional loss.

#765- Paramyotonia congenita in Zambia: A case report with broader implications for rare disease capacity building in sub-Saharan Africa

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**Introduction:** Paramyotonia congenita (PMC) is a rare disease caused by SCN4A gene mutations. We describe a genetically-confirmed case in Zambia and consider the broader need for and impact of rare disease identification and diagnosis in resource-constrained settings.

**Case Report:** A 6-year-old male patient presented to the University Teaching Hospital, Lusaka, Zambia with complaints of extremity stiffness and fatigue exacerbated by exercise. Symptom onset was nine-months. The father and two male siblings had less severe symptoms.

Exam findings included facial stiffness, palpebral fissure narrowing, generalized muscular hypertrophy, hand-grip and thenar percussion myotonia, and a bradyphrenic and lumbering gait. EMG of father's right anterior tibialis confirmed the presence of electrical myotonia.

**Methods:** After parental written informed consent, a blood sample was sent for genetic testing through the International Centre for Genomic Medicine in Neuromuscular Disease.

**Results:** A SCN4A gene mutation was found, alongside a CLCN4 mutation. Given the severe clinical phenotype, the possibility of the CLCN4 mutation as a modifying factor is under further investigation. Analysis of mutations in afflicted family members are forthcoming.

Carbamazepine, available on Zambian government formularies at no patient cost, was prescribed for symptomatic management. At the first follow-up visit, the father noted patient symptom improvement, including ability to ambulate to school.

**Conclusion:** Rare disease treatments may be readily available in resource-constrained settings, but models for identification and diagnosis are lacking. Such models become increasingly urgent as gene-targeted therapies become available. Rare disease research in such settings may also fuel scientific discovery for the benefit of patients globally.

## #817- Novel Mutations in the PLEC Gene: A Case of Epidermolysis Bullosa Simplex with Muscular Dystrophy

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**Introduction/Background:** Plectin is a giant cytoskeleton-crosslinker protein that connects actin microfilaments, microtubules, and intermediate filaments. Mutations in the *PLEC* gene lead to disorganization of myofibrils and sarcomeres, and phenotypically are associated with epidermolysis bullosa simplex (EBS) with muscular dystrophy.

**Case Report:** A 21-year-old woman presented with progressive bilateral upper extremity weakness. She was born with EBS with significant airway involvement and mechanical blistering on her hands and feet. She noted bilateral upper extremity proximal weakness at 15 years of age, which continued to progress over time, limiting her ability of carrying and lifting. On exam, she had bilateral ptosis without limitations of extraocular movements, mild lower facial weakness, and preferential weakness of biceps (3/5 in biceps, 4/5 triceps, 4/5 wrist extension/flexion, 4/5 finger flexion/extension) and mild distal lower extremity weakness. Electromyography exhibited low amplitude, polyphasic motor unit action potentials with early recruitment, consistent with myopathy. Interestingly, there was suggestion of muscle membrane irritation on EMG. Low frequency repetitive nerve stimulation of the right median nerve showed significant amplitude decrement. She underwent sequencing of the *PLEC* gene, revealing variants in c.4687C>T (p.Gln1563) and c.5251C>T (p.Gln1751), neither of which have been previously reported, but both were classified as pathogenic due to their creation of premature stop codons, resulting in expected loss of protein function. She was trialed on pyridostigmine and amifampridine with minimal benefit.

**Summary/Conclusion:** These novel mutations in the *PLEC* gene expands our knowledge of plectinopathies and their heterogenous clinical phenotypes. Clinical trial examining new therapies for this spectrum of disorders is ongoing.

## Academic Registries and Patient Organizations

### #753- Age at loss of ambulation in patients with DMD from the STRIDE Registry and the CINRG Natural History Study: a matched cohort analysis

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**Introduction:** STRIDE (NCT02369731) is an ongoing registry providing data on ataluren use in nonsense mutation Duchenne muscular dystrophy (nmDMD) patients.

**Objectives:** We examined if nmDMD patients receiving ataluren+standard of care (SoC) in the STRIDE Registry experienced a delay in age at loss of ambulation (LOA) versus DMD patients receiving SoC alone in the CINRG Duchenne Natural History Study (NCT00468832).

**Methods:** Data were extracted on January 31, 2022. Propensity score matching identified STRIDE and CINRG patient cohorts (N=260) comparable in established predictors of disease progression: age at first symptoms; age at initiation of corticosteroid use; duration of deflazacort use; and duration of other corticosteroid use. Kaplan–Meier analyses were used to estimate age at LOA.

**Results:** The mean (SD) ages at first symptoms in the STRIDE and CINRG cohorts (N=260 per cohort) were 2.8 (1.7) and 2.8 (1.5) years, respectively. Most patients (STRIDE vs CINRG) received corticosteroids for ≥12 months (85.0% vs 83.8%), with a similar proportion receiving deflazacort (47.7% vs 44.2%) or other corticosteroids (41.9% vs 43.5%). In the STRIDE cohort, 26.5% (69/260) of patients lost ambulation compared with 54.6% (142/260) of patients in the CINRG cohort. The median (95% confidence interval) ages at LOA (STRIDE vs CINRG) were 17.9 (14.8, not estimable) and 12.5 (12.0, 13.5) years, respectively. Kaplan–Meier analyses showed that ataluren+SoC delayed age at LOA compared with SoC alone ( $p<0.0001$ ).

**Conclusions:** These Kaplan–Meier analyses showed that in routine clinical practice ataluren+SoC delayed age at LOA by 5.4 years compared with SoC alone in nmDMD patients.

## #754- Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Natural History Study: a matched cohort analysis

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Word count=245/250

**Introduction:** STRIDE (NCT02369731) is an ongoing, multicenter, observational registry providing data on ataluren use in nonsense mutation Duchenne muscular dystrophy (nmDMD) patients in routine clinical practice.

**Objectives:** We investigated if nmDMD patients receiving ataluren+standard of care (SoC) in the STRIDE Registry experienced a lesser decline in pulmonary function versus DMD patients receiving SoC alone in the CINRG Natural History Study (NCT00468832).

**Methods:** Data were extracted on January 31, 2022. Propensity score matching identified STRIDE and CINRG patient cohorts (N=260) comparable in established predictors of disease progression: age at first symptoms; age at initiation of corticosteroid use; duration of deflazacort use; and duration of other corticosteroid use. Kaplan–Meier analyses were used to estimate ages at %-predicted forced vital capacity (FVC) <60% and <30%.

**Results:** The mean (standard deviation) ages at onset of first symptoms (STRIDE vs CINRG; N=260 per cohort) were 2.8 (1.7) and 2.8 (1.5) years, respectively. Most patients (STRIDE vs CINRG) received corticosteroids for ≥12 months (85.0% vs 83.8%), with a similar proportion receiving deflazacort (47.7% vs 44.2%) or other corticosteroids (41.9% vs 43.5%). Median (95% confidence interval [CI]) ages at %-predicted FVC <60% (STRIDE vs CINRG) were 17.7 (16.8, not estimable) and 15.3 (14.9, 16.5) years, respectively ( $p=0.0053$ ). Median (95% CI) ages at %-predicted FVC <30% (STRIDE vs CINRG) were not estimable and 22.5 (20.3, 25.4) years, respectively ( $p=0.0008$ ).

**Conclusions:** These interim registry data suggest that treatment with ataluren+SoC in routine clinical practice slows disease progression in pulmonary function in nmDMD patients.



#794- MGBase: The launch of an international electronic database for patients with Myasthenia Gravis

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**Introduction:** There is no globally accessible Myasthenia Gravis (MG) database for real world outcomes research. Longitudinal outcome data including physician reported, patient-reported and safety outcomes are limited in MG.

**Objective:** To develop and implement the first international observational database for patients with MG to advance collaborative outcome-based research and improve quality of care.

**Design/Methods:** MGBase was developed from the successful Multiple Sclerosis registry, MSBase (>80,000 patients), with support of the MSBase Foundation. This leverages existing IT infrastructure, data security, privacy compliance and governance structures of MSBase. A minimum data set and extended options enable data quality.

Designed for use during outpatient consultations, MGBase provides a longitudinal display of the patient disease course, therapies and outcomes. The development of MGBase was guided by international MG experts. Members of this group have subsequently formed the MGBase scientific leadership group responsible for determining the overall direction and scope of the MGBase registry.

**Results:** MGBase launched in December 2021 in Australian pilot centers. By August 2022 there were 53 patients enrolled, with mean age of 59 years (67% male), mean disease duration of 9.7 years. Disease subtype was AChR += 29, MuSK +=3, seronegative = 14, unknown =3. Longitudinal data (yearly outcomes, treatment and safety) are available.

**Conclusions:** MGBase is the first observational international registry launched for patients with MG. The MGBase registry is dedicated to evaluating outcomes data in MG and making this available for scientific and health outcomes research within an international collaboration. Updated data will be presented at the conference.

## #799- Patients in the Pompe Registry Who Switched From Alglucosidase Alfa to Avalglucosidase Alfa: Real-world experience

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**Introduction:** Avalglucosidase alfa (AVA), a recombinant human acid  $\alpha$ -glucosidase enzyme replacement therapy, has marketing authorization in several countries for infantile-onset (IOPD) and/or late-onset Pompe disease (LOPD).

**Objectives:** Describe characteristics of IOPD and LOPD patients who switched from alglucosidase alfa (ALG) to AVA enrolled in the international, observational, voluntary Pompe Registry (NCT00231400).

**Methods:** For this analysis, patients had  $\geq 1$  ALG record immediately pre-switch to AVA. Demographic and treatment histories were summarized. Respiratory, ambulatory, and biomarker data were assessed pre- and post-switch for LOPD only.

**Results:** As of April 7, 2023, 119 patients were identified (LOPD, 104 [87%]; IOPD, 15 [13%]). Females: LOPD 49 (47%); IOPD: 9 (60%). Patients switched to AVA at mean  $\pm$  SD age: LOPD  $44.0 \pm 21.86$  (range, 1.0–83.0) y; IOPD:  $9.9 \pm 4.31$  (range, 3.0–17.6) y. Pre-switch, 59 [57%] LOPD and 10 [67%] IOPD patients had received ALG for  $\geq 5$  y. For LOPD, last assessments pre-switch were upright FVC % predicted:  $59.5 \pm 23.71$  (n=84), 6MWT:  $351.3 \pm 160.03$  m (n=52), urine Hex4:  $9.9 \pm 17.07$  mmol/mol creatinine (n=62), and serum CK:  $542.0 \pm 454.93$  U/L (n=81). Mean changes in LOPD patients with both pre- and up to 1-y post-switch assessments showed stabilization in respiratory and ambulatory function, and biomarker improvement.

**Conclusions:** The Pompe Registry continues to accrue data for patients switching from ALG to AVA, which will support our understanding of AVA's effectiveness on respiratory and ambulatory outcomes and biomarker levels in the real-world. **Funding:** Sanofi.

## #841 - CHANGE IN CONCOMITANT THERAPIES FOR GENERALIZED MYASTHENIA GRAVIS IN PATIENTS RECEIVING ECULIZUMAB: A RETROSPECTIVE ANALYSIS OF REGISTRY DATA

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Registry change in concomitant ISTsNMSG 2023 encore abstract

**Introduction:** A range of treatments are available for patients with generalized myasthenia gravis (gMG) such as typical immunosuppressive therapies and complement C5 inhibitors, including eculizumab.

**Objective:** To assess concomitant therapy use at and after eculizumab initiation in patients with gMG.

**Methods:** US patients enrolled in a global gMG registry that collects data on eculizumab use were included if they were treated with eculizumab for  $\geq 1$  year and had data on concomitant therapy use 12 months before eculizumab initiation. Azathioprine (AZA), mycophenolate mofetil (MMF), IVIg/plasma exchange (PLEX), and oral corticosteroid use at initiation of and during eculizumab treatment were analyzed. Data cutoff was July 5, 2022.

**Results:** Of the 94 patients included, 25 (27%), 40 (43%), 25 (27%) and 4 (4%) were receiving zero, one, two, or three concomitant therapies investigated at eculizumab initiation, respectively. Nine (10%) patients received AZA, 26 (28%) MMF, 19 (20%) IVIg/PLEX and 47 (50%) oral corticosteroids. In 57 (61%) patients, the number of concomitant therapies did not change after eculizumab initiation. The number of concomitant therapies decreased in 24 (26%) patients. Thirteen (14%) patients received more treatments after eculizumab initiation. Of the patients using each treatment at eculizumab initiation, AZA was discontinued in 2/9 (22%) patients, MMF in 8/26 (31%), IVIg/PLEX in 5/19 (26%) and oral corticosteroids in 11/47 (23%).

**Conclusions:** One or more concomitant therapy was discontinued in approximately one quarter of patients with gMG treated with eculizumab, providing evidence from clinical practice that eculizumab may enable patients with gMG to reduce concomitant therapies.

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Pharmaceuticals, Inc., argenx, Cabaletta Bio, Inc., CSL Behring, Grifols, S.A., Ra Pharmaceuticals, Inc. (now UCB S.A.), Immunovant, Inc., Momenta Pharmaceuticals, Inc., and Viela Bio, Inc. (Horizon Therapeutics plc). **TM** has no disclosures.

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**HK** was an employee of Alexion, AstraZeneca Rare Disease at time of study.

**BW** is an employee of Alexion, AstraZeneca Rare Disease.

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## #815- Introduction of the Peripheral Neuropathy Research Registry

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**Information and Objectives:** Peripheral polyneuropathy (PN) is a condition that affects approximately 8% of the population over 55 in the United States, which is often associated with intense neuropathic pain. In order to advance the knowledge about PN and to develop more efficient treatments, researchers need to have access to both clinical data and biospecimen for laboratory testing. In order to boost PN research efforts, the Foundation for Peripheral Neuropathy (FPN) started the Peripheral Neuropathy Research Registry (PNRR) to have both data and biospecimen readily available for researchers.

**Methods:** The PNRR data set includes neurological examination, Nerve Conduction Studies, laboratory testing results, as well as patient history questionnaire that catalogues PN symptoms and their severity, medication intake and medical and family history. In addition, plasma, serum and DNA are collected from each patient and stored in the biorepository.

**Results:** Currently, 1450 patients with idiopathic PN are enrolled in the database, 660 with diabetic PN, 150 with HIV-induced PN and 185 with Chemotherapy-induced PN. DNA was collected for all of them, and for 1650 serum and plasma is also available.

**Discussion:** The Foundation for Peripheral Neuropathy (FPN) makes both biospecimen and data available to researchers who want to advance the knowledge about PN. Requests for either biospecimen or data access can be submitted via the FPN website through the PNRR portal for researchers <https://redcap.uits.iu.edu/surveys/?s=XLX8APCJWY>

## #811- Comparison of Nerve Conduction Studies: Prediabetes, Type 2 Diabetes, Metabolic Syndrome and Cryptogenic Sensory Neuropathy

Morgan Hamersky, Simone Thomas, Drs. Ahmet Höke, Amro Stino, Heyrettin Okut, and Mazen M. Dimachkie

**Background:** Diabetes mellitus (DM) is the most common identifiable etiology for polyneuropathy. Most patients with diabetic peripheral neuropathy (DPN) and cryptogenic sensory peripheral neuropathy (CSPN) demonstrate axonal injury, with some data suggesting increased likelihood of demyelination in DPN.

**Objectives:** In this study, we evaluated electrodiagnostic (EDX) parameters across the glycemic spectrum in patients with and without metabolic syndrome.

**Methods:** The Peripheral Neuropathy Research Registry is a cohort of well characterized patients with DPN and CSPN. 994 patients were grouped based on glycemia (type 2 diabetes, prediabetes, or normoglycemia) and presence or absence of metabolic syndrome. We evaluated peroneal motor and sural sensory nerve EDX data normalized across institutions, including conduction velocities, action potential amplitudes, and latencies. The normoglycemic CSPN cohort without metabolic syndrome served as disease control.

**Results:** Both DM and metabolic syndrome were more likely to associate with abnormal NCS findings. DM patients had significantly slowed peroneal motor conduction velocities, reduced sural sensory nerve action potential amplitude, and reduced sural nerve velocities. DM subjects were more likely to have both axonal and demyelinating pathology compared to CSPN subjects. Prediabetic subjects did not differ significantly from CSPN subjects on EDX parameters. Metabolic syndrome was associated with significant slowing of conduction velocity and reduction of action potential amplitude of both sural and peroneal nerves when compared to those without metabolic syndrome.

**Conclusions:** DPN appears to associate with more advanced axonal and demyelinating changes on EDX studies as compared to CSPN, particularly in the presence of metabolic syndrome.

#802- Prevalence of Neuropathies and amyotrophic lateral sclerosis among adults in the United States: A cross-sectional study using the All of Us Research Program Database

Adeel S. Zubair<sup>1</sup>, Shani Evans<sup>1</sup>, Bhaskar Roy<sup>1</sup>

1. Yale School of Medicine, Department of Neurology, New Haven, CT, USA

**Introduction:** The All of Us research program by the National Institutes of Health (NIH) was created to build a diverse health database of patients across the United States, aiming to represent the diversity of the population, including race, ethnicity, sex, gender, and sexual orientation.

**Objectives:** To examine the prevalence of amyotrophic lateral sclerosis (ALS) and neuropathies using the inclusive and diverse All of Us research program.

**Methods:** A cross-sectional analysis utilizing the electronic health records (EHRs) of 369,297 All of US adult participants was performed. Participants with a neuropathy diagnosis were identified by observational medical outcome partnership (OMOP) concept IDs for each condition, which includes Systemized Nomenclature of Medicine (SNOMED) and International Classification of Diseases (ICD) codes.

**Results:** This is ongoing research. The initial analysis reflected a similar prevalence of ALS (0.038 percent (95% CI 0.032-0.045)) based on the most recent estimate from the *Global Burden of Disease Study*, but the prevalence of chronic inflammatory demyelinating polyneuropathy (0.084% [95% CI 0.075-0.094]) was higher, and prevalence of diabetic neuropathy (2.7% [95% CI 2.7-2.8]) was lower than previous reports.

**Conclusions:** Updated prevalence of ALS and neuropathies based on a US-based database is important to understand the disease burden of these conditions. The differences noted in terms of the prevalence of CIDP and diabetic neuropathy can be specific to this database, but may also reflect increased awareness and diagnosis of CIDP, and further investigations are warranted.



A detailed watercolor illustration of pink lilies and green foliage. The lilies are in various stages of bloom, with some fully open and others as buds. The leaves are rendered with soft, painterly textures in shades of green and grey. The background is a light, neutral tone.

# Neuromuscular Study Group

24<sup>TH</sup> ANNUAL SCIENTIFIC MEETING

ORLANDO, FLORIDA | SEPTEMBER 22-24, 2023



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# Welcome



On behalf of your Neuromuscular Study Group (NMSG), we would like to welcome each of you to the 24th Annual Neuromuscular Study Group Scientific Meeting.

As we prepare to embark on this year's conference, we cannot help but look back with pride at the resounding success of our 2022 meeting in Italy. It was an extraordinary event, and we are thrilled to share that it marked our largest attendance to date with over 225 attendees with 141 submitted abstracts. After two years of adapting to online meetings, coming together in person once again was a great atmosphere rekindling of scientific exchange and networking.

The infamous Shark Tank session has gained momentum and we will host our 5th event during the meeting with 3 proposals being presented. The winner will receive a \$10K grant to use towards their study. Last year's winners will be present at the meeting, and we look forward to learning how their funded proposals have progressed.

We are proud to continue to fund our Neuromuscular Research 2-year Fellowship program partnering with the American Brain Foundation. Both of our current Fellows will be presenting during the meeting.

As the Co-Chairs of the Neuromuscular Study Group, we would like to thank this year's planning committee with W. David Arnold serving as chair for putting together an excellent agenda that covers such a broad range of topics and interests within the neuromuscular field. This is a volunteer committee and they have worked especially hard to make the Young Investigator session new and exciting (and not scary!) Our heartfelt gratitude to the planning committee and to each chosen presenter for their invaluable contributions to making our conference such a success.

This year we continue to have industry involvement from both Europe and the U.S., many supporting the NMSG for the first time. Thank you so much to our sponsors for the support, please stop by their tables and look for their abstracts in the poster session. All the accepted abstracts are published in the current RRMNF Journal.

We also want to thank Liz Paulk, NMSG Administrative Manager, for organizing another successful and large event. The planning committee and Liz all have spent much time planning this year's meeting, making it exciting and fresh for the entire group.



RICHARD J. BAROHN, M.D.  
*Chair, Neuromuscular  
Study Group*  
*Executive Vice Chancellor for  
Health Affairs &  
Hugh E. and Sarah D. Stephenson  
Dean, School of Medicine  
University of Missouri*



PROF MICHAEL G. HANNA, M.D.  
*Co-chair, Neuromuscular  
Study Group*  
*Director, University College London  
Institute of Neurology*



# Committees

## NMSG EXECUTIVE COMMITTEE

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University of Missouri

*Co-Chairman*

**Michael Hanna, M.D.**

UCL Institute of Neurology

*Chairman Emeritus*

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University of Rochester Medical Center

*Investigator Members*

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Massachusetts General Hospital

**Valeria Sansone, M.D., Ph.D.** (outgoing)

Massachusetts General Hospital

**Michael Hehir, M.D.**

University of Vermont

**John Vissing, M.D.** (incoming)

Copenhagen Neuromuscular Center

*Evaluator Member*

**Melissa McIntyre, DPT**

University of Utah

*Study Coordinator Member*

**Marie Wencel, CCRP**

University of California, Irvine

*Bio Statistician*

**Michael McDermott, Ph.D.**

University of Rochester Medical Center

*Coordination Center Director*

**Rabi Tawil, M.D.**

University of Rochester Medical Center

*Treasurer*

**Mazen Dimachkie, M.D.**

University of Kansas Medical Center

## 2023 PLANNING COMMITTEE

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*NMSG Chair*

**Richard Barohn, M.D.**

University of Missouri

*NMSG Co-Chair*

**Michael Hanna, M.D.**

University College London

# Information

## WIFI

The NMSG has a special wifi access for meeting attendees.

This network can be used in the Conference Center.

Network name: Neuromuscular2023 | Password: StudyNM23

Wifi is also available in the hotel.

Network name: Caribe Network | Password: Room number, first and last name

## SATURDAY DINNER

Dinner on Saturday night will be in the Caribbean VI and VII Ballroom after the conclusion of the Key Note Speaker. After dinner we will have dessert and a reception outside at the Boca Patio.

Dress for the evening is business attire.

All are welcome.

## SPEAKERS/PRESENTERS

Please bring your presentation to Amardeep Gill, our onsite AV expert, at the back of the Caribbean IV general session room the morning of your session.

Our technical staff will assist you with any audio/visual needs you may have. You will not need your own laptop as we have one available.

## POSTERS

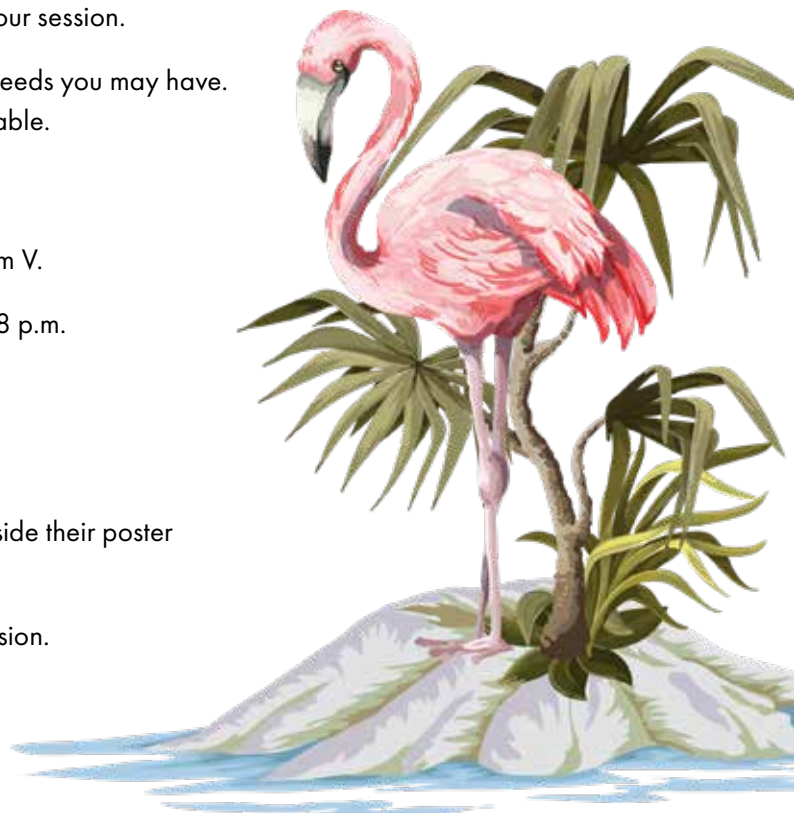
The poster exhibition is located in the Caribbean Ballroom V.

Walk through poster session is Friday, September 22, 6-8 p.m.

Please set up your poster in the Caribbean Ballroom V after 7 p.m. on Thursday, or first thing Friday morning. Posters will be displayed all day and evening on Friday.

Important note: Poster presenters are requested to be beside their poster during the walk through session.

Please remove your poster after the conclusion of the session.





# Agenda

## 24<sup>TH</sup> ANNUAL NEUROMUSCULAR STUDY GROUP SCIENTIFIC MEETING



### DAY 1: FRIDAY, SEPTEMBER 22

6:30-8 a.m.	Buffet Breakfast and Check-In   <i>Caribbean VI and VII</i>
8-8:20 a.m.	Welcome and State of the Neuromuscular Study Group Dr. Richard Barohn and Prof Michael Hanna   <i>Caribbean III and IV</i>

### SESSION I: MOTOR NEURON AND NEUROMUSCULAR JUNCTION Heidi Fuller, M.D., Moderator | *Caribbean III and IV*

8:20-8:40 a.m.	Unravelling Inflammatory Neuropathies Simon Rinaldi, MBChB, Ph.D.   <i>University of Oxford</i>
8:45-9:05 a.m.	Towards Clinical Trial Readiness for Charcot Marie Tooth Neuropathies David Hermann, MBBCh   <i>University of Oxford</i>
9:10-9:30 a.m.	Respiratory Updates in CANVAS Riccardo Zuccarino, M.D.   <i>NEMO Milan</i>
9:35-9:55 a.m.	Recent Learnings from Non-Coding Genome Investigations Stephan Zuchner, M.D., Ph.D.   <i>University of Miami</i>
10-10:15 a.m.	Refreshment/Exhibitor Break
10:15-10:35 a.m.	Expanding Therapeutic Options in Myasthenia Gravis James Howard, M.D.   <i>The University of North Carolina at Chapel Hill</i>
10:40-11 a.m.	Updates on ALS Jon Katz, M.D.   <i>Sutter Health, California Pacific Medical Center, The Forbes Norris MDA/ALS Research and Treatment Center</i>

### SESSION II: FLASH PRESENTATIONS Dr. Michael Pulley, Moderator | *Caribbean III and IV*

11:05-11:15 a.m.	Investing to Save: Evaluation of Unplanned Hospital Admissions of Neuromuscular Patients in Greater Manchester, UK Marwah Almadhi, BSc Biomedical Sciences, MBChB Medicine (current)   <i>University of Manchester</i>
11:17-11:27 a.m.	Measuring Adverse Event Burden in Myasthenia Gravis: Retrospective Validation of the Adverse Event Unit (AEU) with MGTX Trial Data Michael Hehir, M.D.   <i>University of Vermont</i>
11:29-11:39 a.m.	A Systematic Review and Meta-Analysis of the Placebo Effect in Inclusion Body Myositis Elie Naddaf, M.D.   <i>Mayo Clinic</i>
11:41-11:51 a.m.	The Inclusion Body Myositis Health-Index (IBM-HI): Development of a Novel, Disease Specific Patient-Reported Outcome Measure for IBM in Clinical Trials Shaweta Khosa, M.D.   <i>University of Rochester, Center of Health and Technology Outcomes Division (CHeT)</i>
11:53 a.m.- 12:03 p.m.	Relationships of Lower Leg Fat Fraction Among Antagonistic and Synergistic Muscles and a Potential Fat Fraction Threshold for Functional Performance in Myotonic Dystrophy Type 1 Zhihao He, MS   <i>University of Florida</i>
12:05-12:15 p.m.	Mycophenolate is Better Tolerated Than Azathioprine in Myasthenia Gravis Katy Dodd, MBChB, MRCP   <i>University of Manchester</i>



12:17-12:27 p.m.	<b>A UK Experience of Symptomatic Treatment of Myotonia with Lamotrigine</b> Iwona Skorupinska, MSc, BSc   <i>University College London</i>
12:30-1:30 p.m.	<b>Lunch</b>   <i>Caribbean VI and VII</i> <b>Neuromuscular Study Group Executive Committee Meeting Breakout Lunch</b>   <i>Governor's Board Room</i>
<b>SESSION III: PLATFORM PRESENTATIONS</b> Kris Kelly, DPT, MS, EdM, Moderator   <i>Caribbean III and IV</i>	
1:30-1:45 p.m.	<b>Improving Diagnostic Rates for Mitochondrial Diseases Using Enhanced WGS Analysis and RNA-seq</b> William Macken, M.D., Ph.D.   <i>University College London</i>
1:50-2:05 p.m.	<b>MEND: MExiletine versus lamotrigine in Non-Dystrophic Myotonia</b> Vinojini Vivekanandam, MBBS(Hons)   <i>University College London, Queen Square</i>
2:10-2:25 p.m.	<b>Scoliosis Progression in Type II SMA at the Time of Treatment: A Comparative Study with Untreated Patients</b> Giorgia Coratti, Ph.D.   <i>Catholic University of Sacred Heart</i>
2:30-2:45 p.m.	<b>Remote Monitoring and Management of Myasthenia Gravis (REMOTE-MG): A Pilot Feasibility Study</b> Michael Hehir, M.D.   <i>University of Vermont</i>
2:50-3 p.m.	<b>Refreshment/Exhibitor Break</b>
<b>SESSION IV: YOUNG INVESTIGATOR/EVALUATOR/COORDINATOR *ALL NEW*</b> Session Moderators: Dr. W. David Arnold, Dr. Karen Suetterlin, Dr. Katherine Dodd, Dr. Heidi Fuller, Prof Valeria Sansone, Marie Wencel, CCRP <i>Caribbean III and IV</i>	
3-5 p.m.	<b>How to Give an Effective Elevator Pitch</b> <b>Failing Well, Overcoming Rejections, Criticisms and Changing Direction</b> <b>Networking</b>
<b>POSTER SESSION</b> <i>Caribbean V</i>	
6-8 p.m.	<b>Poster Walk Through and Reception</b> <b>Reception</b>
8-9 p.m.	<b>Dinner</b>   <i>Caribbean VI and VII</i>
9-11:30 p.m.	<b>Reception</b>   <i>Atrium East, Main Hotel Lobby, Lower Level</i>

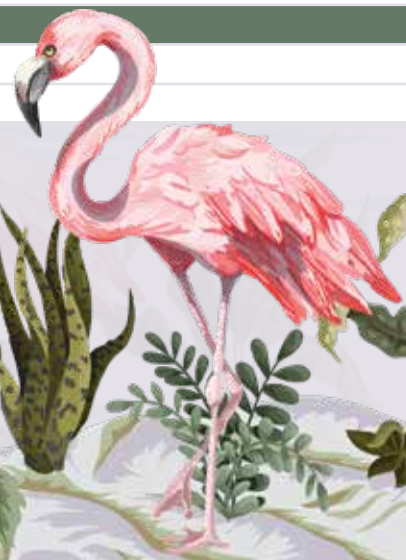


## DAY 2: SATURDAY, SEPTEMBER 23

7-8 a.m.	<b>Buffet Breakfast</b>   <i>Caribbean VI and VII</i>
8-8:15 a.m.	<b>Opening</b> Dr. Richard Barohn and Prof Michael Hanna   <i>Caribbean III and IV</i>
<b>SESSION V: BIOMARKERS</b> Donovan Lott, PT, Ph.D., CSCS, Moderator   <i>Caribbean III and IV</i>	
8:15-8:35 a.m.	<b>Shear Wave Elastography in Neuromuscular Disease</b> Lisa Hobson-Webb, M.D.   <i>Duke University</i>
8:40-9 a.m.	<b>Unveiling the Hidden Regulators: Circulating MicroRNAs as Biomarkers in Myasthenia Gravis</b> Professor Anna Rostedt Punga, M.D., Ph.D.   <i>Uppsala University</i>
9:05-9:25 a.m.	<b>Neurofilament as a biomarker in ALS clinical trials</b> Robert Bowser, Ph.D.   <i>Barrow Neurological Institute</i>
9:30-9:50 a.m.	<b>Alternative Splicing DM</b> Eric Wang, Ph.D.   <i>University of Florida</i>
9:55-10:15 a.m.	<b>MRI as a Biomarker in the Muscular Dystrophies</b> Glenn Walter, Ph.D.   <i>University of Florida</i>
10:15-10:30 a.m.	<b>Refreshments/Exhibitor Break</b>
<b>SESSION VI: AGING</b> W. David Arnold, M.D., Moderator   <i>Caribbean III and IV</i>	
10:30-10:50am	<b>Proteomic Analysis of Differentially Vulnerable Synaptic Populations to Identify Regulators of Stability</b> Thomas Wishart, BSc., M.B.A., Ph.D.   <i>University of Edinburgh</i>
10:55-11:15am	<b>Motor Unit Magnetic Resonance Imaging (MUMRI) in Ageing Skeletal Muscle</b> Matthew Birkbeck, Ph.D.   <i>Newcastle University/Newcastle Upon Tyne Hospitals NHS Foundation Trust</i>
11:20-11:40am	<b>Clinical Aspects of Sarcopenia</b> Roger Fielding, Ph.D.   <i>Tufts University</i>
11:45 a.m.-1 p.m.	<b>Lunch</b>   <i>Caribbean VI and VII</i>
<b>SESSION VII: EXERCISE</b> Dr. Miguel Chuquilin, Moderator   <i>Caribbean III and IV</i>	
1-1:20 p.m.	<b>Effect of exercise on functional outcomes and disease pathophysiology in DM1</b> Elisa Duchesne, PHT, Ph.D.   <i>Université du Québec à Chicoutimi</i>
1:25-1:45 p.m.	<b>Exercise in SMA: More Than Just an Intervention</b> Jackie Montes, PT, EdD, NCS   <i>Columbia University Irving Medical Center</i>
1:50-2:10 p.m.	<b>Exercise as medicine for DMD</b> Tanja Taivassalo, Ph.D.   <i>University of Florida</i>
2:15-2:35 p.m.	<b>Exercise, Rehabilitation and Physical Activity in Charcot-Marie-Tooth Disease</b> Gita Ramdharry, Ph.D.   <i>University College London</i>
2:40-3:10 p.m.	<b>Refreshments/Exhibitor Break</b>
<b>SPONSOR PRESENTATIONS</b> W. David Arnold, M.D., Moderator   <i>Caribbean III and IV</i>	
3:10-3:30pm	<b>NMJ damage in MG: Point of no return or potential for repair?</b> James F. Howard, Jr., M.D., FAAN   <i>The University of North Carolina at Chapel Hill</i>
3:35p-3:55pm	<b>Innovation in the Development of Treatments for Neuromuscular Diseases</b> Jeffrey Guptill, M.D., MA, MHS, FAAN   <i>Efgartigimod Neuromuscular Franchise Lead Clinical Development, Argenx</i>
4:00-4:20pm	<b>Advancing Precision Genetic Medicine Through Innovative Technologies for Neuromuscular Diseases</b> Teji Singh, M.D.   <i>Sarepta Therapeutics</i>
4:25-4:45pm	<b>Addressing unmet needs in FSHD: Data from the losmapimod Phase 2 trial</b> Olga Mitelman, M.D.   <i>Head of Medical Affairs, Fulcrum Therapeutics</i>
4:50-5:10pm	<b>Lambert-Eaton Myasthenic Syndrome is Underrecognized in Small Cell Lung Cancer: An Analysis of Real-World Data</b> Nicholas Streicher, M.D., MPH   <i>MedStar Georgetown University Hospital</i>
5:15-5:35pm	<b>At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development, and manufacture of health care products, including innovative medicines and vaccines</b>
<b>ROBERT C. GRIGGS ANNUAL NMSG KEYNOTE SPEAKER</b>   <i>Caribbean III and IV</i>	
7:30-8:30 p.m.	<b>The Circle of Translation</b> Professor Mary M. Reilly   <i>UCL Queen Square Institute of Neurology</i>
<b>8:30-9:30 p.m.</b> <b>Dinner</b>   <i>Caribbean VI and VII</i>	
9:30-11 p.m.	<b>Evening Reception</b>   <i>Boca Patio</i>

**DAY 3: SUNDAY, SEPTEMBER 24**

7-8 a.m.	<b>Buffet Breakfast</b>   <i>Caribbean VI and VII</i>
8-8:10 a.m.	<b>Opening</b> Dr. Richard Barohn and Prof Michael Hanna   <i>Caribbean III and IV</i>
<b>SESSION VIII: NMSG YOUNG INVESTIGATORS PROJECTS</b> Dr. Karen Suetterlin, Moderator   <i>Caribbean III and IV</i>	
8:10-8:25 a.m.	<b>Neuromuscular Ultrasound as a Biomarker to Improve Clinical Trial Readiness in Charcot Marie Tooth Neuropathies</b> Tyler Rehbein, M.D., 2022 NMSG Fellow   <i>University of Rochester</i>
8:30-8:45 a.m.	<b>Development of Novel Imaging Biomarkers for use in Pediatric Facioscapulohumeral Muscular Dystrophy</b> Natalie Katz, M.D., 2023 NMSG Fellow   <i>Duke University</i>
8:50-9:05 a.m.	<b>2022 Shark Tank Award Update: Quantifying Idiopathic Inflammatory Myopathy-Associated Cancer Risk via Comprehensive Phenotyping of a Large UK-Wide Cohort</b> Alex Oldroyd, MBChB, Ph.D., MSc, MRCP   <i>University of Manchester</i>
9:10-9:25 a.m.	<b>2022 Shark Tank Award Update: Predictive Models in Spinal Muscular Atrophy Treated Patients Using Machine Learning</b> Georgia Coratti, Ph.D.   <i>Pediatric Neurology and Centro Clinico Nemo Rome</i>
<b>SHARK TANK SESSION</b> Aziz Shaibani, M.D., FACP, FAAN, FANA, Moderator   <i>Caribbean III and IV</i> Shark Panel: Mazen Dimachkie, M.D., Amanda Guidon, M.D., MPH, Laurie Gutmann, M.D.	
9:30-10:40 a.m.	<b>Perceived Fatigability Tracker: Improving Assessment to Enhance Spinal Muscular Atrophy (SMA) Patient Outcomes</b> Rafael Rodriguez-Torres DPT   <i>Columbia University Irving Medical Center</i>
	<b>Are patients with IIM at a greater risk of developing PCC than healthy controls at six months after COVID infection</b> Tulika Chatterjee, M.D.   <i>University of Illinois College of Medicine at Peoria, IL</i>
	<b>LITEBulb SMA - Lingual Intervention of Tongue Exercises for BULBar SMA</b> Carla Zingariello, DO   <i>University of Florida College of Medicine</i>
10:40-10:55 a.m.	<b>Refreshments/Exhibitor Break</b>
<b>SESSION IX: EMERGING PHENOTYPES</b> Dr. Katy Dodd, Moderator   <i>Caribbean III and IV</i>	
10:55-11:20 a.m.	<b>Neuromuscular Implications of Placebo Research</b> Aziz Shaibani, M.D., FACP, FAAN, FANA   <i>Nerve and Muscle Center of Texas</i>
11:25-11:45 a.m.	<b>Treating Adults with SMA in the UK</b> James Lilleker, MBChB, Ph.D.   <i>University of Manchester</i>
11:50 a.m.- 12:10 p.m.	<b>Neuromuscular Complications of Cancer Immunotherapy</b> Amanda Guidon, M.D., MPH   <i>Mass General Hospital, Harvard University</i>
12:15-12:35 p.m.	<b>Pediatric FSHD, overview and gaps in knowledge</b> Katherine Mathews, M.D.   <i>University of Iowa Carver College of Medicine</i>
12:35-1:45 p.m.	<b>Closing</b>   <i>Caribbean III and IV</i>
	<b>Lunch</b>   <i>Caribbean VI and VII</i>





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JOIN US FOR A POSTER PRESENTATION UNCOVERING NEW DATA REGARDING  
THE PREVALENCE OF LAMBERT-EATON MYASTHENIC SYNDROME (LEMS)  
IN PATIENTS WITH SMALL CELL LUNG CANCER (SCLC)

**Nicholas Streicher, MD, MPH**  
Assistant Professor of Neurology  
Georgetown University Hospital

**2023 Neuromuscular Study Group (NMSG)  
Annual Scientific Meeting**  
Saturday, September 23, 2023  
5:10 PM-5:30 PM | 5-minute Q&A to follow

**We hope to see you at this special presentation.**  
Preregistration is not required. A member of our  
staff will be on-site to assist with check-in.



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This activity is not part of the official scientific program of the NMSG  
and is not available for Continuing Medical Education (CME) credit.



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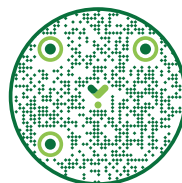
Saturday,  
September 23

**3:35 PM to 3:55 PM**  
Conference Center  
Caribbean III and IV  
Caribe Royal Hotel  
Orlando, FL

## Innovation in the Development of Treatments for Neuromuscular Diseases

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Join us as we discuss novel targets for the treatments of neuromuscular diseases (NMDs).



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Visit us at our exhibit booth

Ig=immunoglobulin; IVIg=intravenous immunoglobulin; SCIg=subcutaneous immunoglobulin.

References: 1. Pfizer Inc. Company fact sheet. Accessed March 10, 2023. <https://www.pfizer.com/news/media-resources/press-kits/corporate-media-kit>. 2. Fortune Business Insights. Report ID: FBI100571. February 2023. Accessed March 10, 2023. <https://www.fortunebusinessinsights.com/industry-reports/immunoglobulins-market-100571>.

PP-CQG-USA-0574

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March 2023

## Advance your diagnosis coding for limb-girdle muscular dystrophy New ICD-10 codes as of October 2022

Have you been using G71.00 (“Muscular dystrophy, unspecified”) or G71.09 (“Other specified muscular dystrophies”) for your LGMD patients? There are more specific codes available.

Support clinical and research communities in ongoing efforts to:

- Understand LGMD epidemiology
- Assess disease progression
- Understand economic burden of LGMD
- Help manage care of patients
- Facilitate reimbursement and patient access when targeted therapies become available in the future

Diagnosis Code	Description	Subtype, if applicable
G71.031	Autosomal dominant LGMD	LGMD1/D
G71.032	Autosomal recessive LGMD due to calpain-3 dysfunction (calpainopathy)	LGMD2A/R1
G71.033	LGMD due to dysferlin dysfunction (dysferlinopathy)	LGMD2B/R2
G71.0340	LGMD due to sarcoglycan dysfunction, unspecified (sarcoglycanopathy)	
G71.0341	LGMD due to alpha sarcoglycan dysfunction (alpha-sarcoglycanopathy)	LGMD2D/R3
G71.0342	LGMD due to beta sarcoglycan dysfunction (beta-sarcoglycanopathy)	LGMD2E/R4
G71.0349	LGMD due to other sarcoglycan dysfunction	LGMD2C/R5* LGMD2F/R6*
G71.035	LGMD due to anoctamin-5 dysfunction (anoctaminopathy)	LGMD2L/R12
G71.038	Other LGMD	
G71.039	LGMD, unspecified	

\*LGMD2C/R5 is caused by mutations in the SGCG gene, which encodes gamma-sarcoglycan. LGMD2F/R6 is caused by mutations in the SGCD gene, which encodes delta-sarcoglycan.

G71.038 is intended for all other forms of autosomal recessive LGMD. G71.039 is intended for patients that do not have a genetically confirmed LGMD diagnosis. If your patient has not yet received genetic testing to confirm their LGMD diagnosis, explore no-charge sponsored genetic testing options.



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## NOW ENROLLING

REGENXBIO, a global leader in AAV gene therapy, is currently enrolling participants in a clinical trial of RGX-202, an investigational, one-time gene therapy for the potential treatment of Duchenne muscular dystrophy (DMD). The clinical trial will evaluate the effect of RGX-202 in boys with DMD between the ages of 4 - 11 years.

### Find a study location near you!

Visit [ClinicalTrials.gov](https://ClinicalTrials.gov) (identifier #NCT05693142) for a full list of trial sites.

Find a study location



### Questions?

If you would like to get in touch with a member of our Patient Advocacy team, you may email us at [Duchenne@regenxbio.com](mailto:Duchenne@regenxbio.com).

If you are a healthcare provider and would like more information on our studies for patients with Duchenne, please contact us at [medinfo@regenxbio.com](mailto:medinfo@regenxbio.com).

**Visit us at our NMSG Booth**



## Transforming Lives. Every Day.

At Alexion, our mission is to transform the lives of people affected by rare diseases and devastating conditions through the development and delivery of innovative medicines, as well as through supportive technologies and healthcare services.

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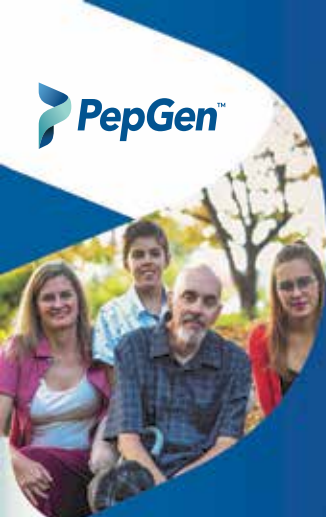


# Committed to Developing a Transformative Therapy for the Treatment of Neuromuscular Diseases (NMDs)

PepGen is advancing the next generation of oligonucleotide therapeutics, revolutionizing the treatment of severe neuromuscular disorders (NMDs). Our enhanced delivery oligonucleotides (EDOs) are engineered to optimize delivery to the affected tissues. Our mission is to deliver transformative therapies to improve the lives of people living with NMDs, their families and the broader community.

Driven by our proprietary EDO platform, we are creating a pipeline of therapies designed to target the root cause of NMDs. PepGen's lead programs are in Duchenne muscular dystrophy and myotonic dystrophy type 1.

Visit our website to learn about our approach, pipeline, and upcoming clinical trials.



**Astellas Gene Therapies is committed to developing innovative genetic medicines for patients with rare neuromuscular disorders.**

Visit our website to learn more!  
[www.astellasgenetherapies.com](http://www.astellasgenetherapies.com)



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**SAVE THE DATE!**  
**25<sup>th</sup> Anniversary NMSG Meeting**  
**September 20-22, 2024**  
**Tarrytown House Estates**  
**Tarrytown, New York, USA**





# Abstracts

Abstracts for research presented at this year's NMSG scientific meeting can be viewed online by scanning the QR code or visiting: [doi.org/10.17161/rnmf.v4i4](https://doi.org/10.17161/rnmf.v4i4)



# Continuing Education

NEUROMUSCULAR STUDY GROUP (NMSG)  
ANNUAL SCIENTIFIC MEETING

September 22-24, 2023  
Orlando, FL

## JOINT ACCREDITATION STATEMENT

In support of improving patient care, this activity has been planned and implemented by Amedco LLC and Neuromuscular Study Group (NMSG). Amedco LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Amedco Joint Accreditation #4008163.

## PHYSICIANS (ACCME) CREDIT DESIGNATION

Amedco LLC designates this live activity for a **12.00 credits** AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.



JOINTLY ACCREDITED PROVIDER™  
INTERPROFESSIONAL CONTINUING EDUCATION

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