therapy for patients with Duchenne muscular dystrophy (DMD) amenable to exon 51 skipping. Safety and tolerability data from the suvodirsen Phase 1 clinical trial (NCT03508947) support the initiation of a Phase 2/3 trial. Wave's planned Phase 2/3 trial for suvodirsen has been selected for the US Food and Drug Administration (FDA) pilot program for complex innovative trial designs. We present the design of the Phase 2/3 trial of suvodirsen in patients with DMD amenable to exon 51 skipping. This is a global, multicenter, randomized, double-blind, placebo-controlled trial to determine the efficacy and safety of suvodirsen in approximately 150 ambulatory male patients 5–12 years of age (inclusive). Key endpoints include change from baseline in dystrophin protein levels and motor function by North Star Ambulatory Assessment over 48 weeks. Two interim analyses will assess dystrophin protein levels from open biopsies of deltoid muscle using western blot. Additional endpoints include assessment of upper/lower limb function, respiratory function, and stride velocity (measured by a wearable device). As part of the design, DMD historical control data will be leveraged to help minimize the number of patients required in the placebo arm to deliver conclusive clinical efficacy results and potentially accelerate study completion. The extent of the clinical efficacy of exon skipping therapies is currently not fully established. With feedback from the FDA and the global DMD community, the innovative design of the Phase 2/3 clinical trial may allow for a more resourceful determination of suvodirsen's clinical efficacy in patients with DMD. It may also inform designs of future rare disease clinical trials.

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Quality of life in patients with Duchenne muscular dystrophy

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To investigate changes of Health Related Quality of Life (HRQOL) measures of patients with Duchenne muscular dystrophy (DMD) with respect to their motor, cardiac and pulmonary function over time. Retrospective review of 542 DMD patients' clinical data pertaining to HRQOL, motor function (Functional Mobility Score/FMS), cardiac function (Left Ventricular Ejection Fraction/LVEF) and pulmonary function (Forced Vital Capacity Percent Predicted/FVC%). The effects of FMS, LVEF, and FVC% on QOL scores over time were analyzed. For boxplots by various categories within each domain, QOL scores were averaged by patient within each category. A repeated measures linear mixed model of the QOL scores on the FMS categories was conducted. Lastly, a paired t-test was used to measure differences between child and parent reported outcomes within each domain. The Generic Core (GC) QOL and the Neuromuscular (NM) QOL decreased with declining motor function for the ambulatory patients ($p<0.0001$), but not for the non-ambulatory patients ($p>0.12$). NM QOL and Emotional QOL decreased with decreasing FVC% ($p<0.0001$). Cardiac function had no effect on any QOL measures. Social QOL and School QOL are not affected by worsening physical, pulmonary or cardiac function in patients with DMD. Apart from emotional QOL ($p=0.2$), patient reported QOL scores were significantly higher than parent reported QOL scores ($p<0.0001$). Declining motor function adversely affects GC QOL and NM QOL in ambulatory patients with DMD. Declining pulmonary function adversely affects NM QOL and Emotional QOL. In general, patient reported QOL scores were higher than parent reported scores.

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Exploring the trainability of working memory and learning in Duchenne muscular dystrophy using computerized memory training

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Duchenne muscular dystrophy (DMD) is an X-linked recessive disease caused by gene mutations, leading to an absence of dystrophin protein isoforms in various tissues including the brain. A lack of dystrophin isoforms in the brain is hold responsible for the cognitive abnormalities in DMD. Especially, working memory problems and learning difficulties are frequently described in DMD, and these are known to have a major influence on academic achievement throughout childhood and adolescence. Previous research in the general population suggests that working memory problems and learning difficulties are trainable by memory programs. Positive and long-lasting results have been described particularly for the computerized Jungle memory program in children and adolescents with ADHD or learning difficulties. The current study aimed to assess the trainability of the dystrophin-associated working memory problems and learning difficulties in five male patients (age range = 10 – 16 years) with DMD, using the computerized Jungle memory program. A single case experimental design (SCED) with an A (non-intervention) B (intervention) A (non-intervention) withdrawal method was used. The study consisted of distinct phases. At baseline (week 0 to 3), patients underwent a short neuropsychological assessment and received psycho-education on working memory problems. Hereafter, the intervention program commenced based on randomization outcomes. At post-test (1 to 3 weeks after the intervention), and at 3 and 8 months follow-up patients repeated the baseline neuropsychological battery. Additionally, a weekly questionnaire on working memory problems was completed by parents throughout the baseline, intervention, and post-test period. Weekly administration outcomes of parents will be assessed by Tau-U analyses for SCED and outcomes of the neuropsychological assessments by reliable change index analyses (RCI). Preliminary results will be presented.

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EP.86

The effect of trunk training on trunk control, upper extremity, and pulmonary function in children with Duchenne muscular dystrophy

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Trunk control is a part of postural control and is necessary for stabilization of the trunk which is essential for the selective movements of the head and extremities. The aim of this study was to investigate the effects of individualized trunk exercises on trunk control, upper extremity, and pulmonary functions in boys with DMD. Twenty-six children with DMD at level 1-5 according to the brooke upper extremity functional classification (BUEFC) were included in the study. They divided two groups (study and control) and their trunk control were assessed by trunk control measurement scale (TCMS). The upper extremity function was assessed by performance of upper limb (PUL) and respiratory functions by pulmonary function test. After the evaluation, the children in the study group were given a training targeting trunk for 8 weeks, 2 days a week, 45 minutes per day in addition to the routine physiotherapy treatment program. Control group was applied routine physiotherapy program at home. Assessments were repeated again after 8 weeks in both groups. The mean age of children was 10.32 ± 5.24 years. According to the comparison of 8th week assessment results of the groups, there were statistically significant improvements in upper extremities functions and trunk control in favor of the study group ($p<0.01$), while no difference was obtained in respiratory functions between the groups ($p>0,05$). In our study, trunk rehabilitation in children with DMD were shown to be effective on trunk control and upper extremity functions. This result suggests that trunk control should be added to the assessments, and

approaches targeting trunk should be provided in the physiotherapy programs of patients with DMD.

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EP.87

MYODA clinical program: composite score for assessing the efficacy of BIO101 (MAS activator) in ambulatory and non-ambulatory Duchenne boys

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The purpose of the clinical program MYODA is to evaluate muscle strength and function in boys suffering from Duchenne Muscular Dystrophy (DMD) under long-term oral administration of BIO101 (20-hydroxyecdysone, MAS activator). Ambulant and non-ambulant DMD boys will be recruited. The heterogeneity of the clinical course of DMD has long been recognised and more recently has been captured in registry studies (Ricotti et al. 2013, 2016, Mercuri et al. 2016). Moreover, the mode of action of BIO101 and the pre-clinical proof-of-concept (PoC) suggest that DMD patients who will benefit from BIO101 is quite broad and that this benefit can be shown in a variety of functions: mobility, strength and respiratory. Due to study size limitation, using multiple outcomes and studies to assess totality of evidence for efficacy and safety is desirable for rare disease drug development. In comparing a new treatment with a control for DMD under a randomized clinical trial setting, each study patient has multiple efficacy outcomes collected over time (NSAA, PUL, 6MWT, MyoPinch, MyoGrip, PEF, FVC). Instead of defining a primary endpoint using a single outcome and identifying several secondary endpoints like most conventional studies, Biophytis presents several approaches to utilize multiple outcomes simultaneously to evaluate BIO101 effect. The resulting procedures should be more powerful to detect the treatment difference than the conventional design and also provide clinically meaningful interpretation on the totality of treatment efficacy evidence (Ricotti et al.2019). Biophytis hypothesizes that a composite score, which covers both muscle strength, skeletal muscle and respiratory functions and captures changes across the loss of ambulation might be best adapted to detect changes across the wide disease spectrum. Biophytis will study how the change in the endpoint may be clinically meaningful. Biophytis will extend the analysis using Matching population from DMD databases.

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Development of clinical trial simulation tool for Duchenne muscular dystrophy through the Duchenne Regulatory Science Consortium

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Developing clinical trial protocols that give definitive answers as to whether potential new therapies are effective for rare diseases is challenging due to the small population sizes, limitations on availability of natural history data and limited understanding of disease progression. In Duchenne muscular dystrophy (DMD) this has contributed to few trials meeting primary endpoints, and led to questions as to how best to evaluate efficacy of therapeutic candidates. The Duchenne Regulatory Science Consortium (D-RSC) is a public-private-partnership that aims to develop quantitative tools to accelerate drug development and seeks approval of such tools through regulatory pathways at FDA (Food and Drug Administration) and EMA (European Medicines Authority) to confirm utility and value. D-RSC is developing a multivariate model-based clinical trial simulation (CTS) tool, based on longitudinal models of endpoints that span the course of disease (velocity of completion of supine to stand test, 4-stair climb test, and 10-meter walk/run test, NorthStar Ambulatory Assessment, forced vital capacity and Brooke scale). Models include covariates that predict differences in DMD progression such as use of steroids, height, weight, genetics and baseline function. D-RSC has integrated data from 14 independent studies using CDISC standards, the largest DMD clinical database currently available. The final analysis data set after exclusions, excluding missing observations, includes 1139 individuals with a total of 24210 observations of the endpoints from 4 to 34 years of age. The CTS tool that will be developed based on the disease progression models will help drug developers determine optimal clinical study characteristics, including selection of endpoints, inclusion criteria, trial design, size and duration. This will allow development of trial protocols using the lowest number of patients and in the least time possible to reach conclusive decisions on drug efficacy.

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EP.89

Clinical trials in young boys and infants with DMD: how do you handle maturation?

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Clinical trials are targeting increasingly younger cohorts of boys with Duchenne muscular dystrophy (DMD) as data suggests earlier intervention may maximize treatment effect. The Gross Motor subtest of the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III), North Star Ambulatory Assessment (NSAA), and 100 meter timed test (100m) have been shown to be useful in quantifying function in this young age group. It is expected that children with DMD will gain function until approximately 7-8 years of age. Recent data suggests that boys with DMD have early gross motor delays and that although they gain skills, they are on a lower trajectory than typical peers. Quantifying the development of infants and children with DMD from a very early age will allow deviations from the expected trajectory to be identified at an earlier age. The purpose of our study was to define the natural history in a continuous cohort from birth to 8 years using the Bayley-III, NSAA, and 100m. One hundred fifty-one boys with DMD ages 0.8 – 8 years of age were evaluated using the Bayley-III (0.8 – 6 years), North Star Ambulatory Assessment (NSAA) (1.5 - 8 years) and the 100 Meter Timed Test (100m) (3.4 – 8 years) as standard of care during regularly scheduled clinic visits. As expected, as a group, boys with DMD have lower gross motor skills that age matched controls. However, steroid exposure significantly improved baseline scores across all outcomes. Longitudinal data on a sub cohort (N=93) was also collected with visits every 3-6 months over 2 years. Natural progression in DMD by age and steroid exposure for each outcome will be presented, as well as regression equations to establish predicted performance for individuals given age and steroid exposure. Predicted 'growth curve' trajectories can be used to determine if the rate of change following an intervention falls outside of expectations for DMD. To our knowledge this is the largest presentation of developmental data on infants and young boys with DMD.

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The relationship between "fear of falling" and physical performance, and quality of life in children with Duchenne muscular dystrophy

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This study was aimed to investigate the fear of falling (FOF) in children with Duchenne muscular dystrophy (DMD) and determine its relation with physical performance parameters and quality of life. Thirty ambulatory boys diagnosed with DMD were participated in the study. Functional status was determined by levels between 1-5 according to brooke lower extremity