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

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

M. Chabane [1], W. Dioh [1], P. Dilda [1], R. Lafont [1], S. Veillet [1], T. Voit [2], S. Agus [1]
[1] *Biophytis, Paris, France;* [2] *UCL Great Ormond Street Instit, Paris, France*

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

J. Larkindale, D. Conrado, D. Corey, K. Romero
Critical Path Institute, Tucson, USA

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

N. Miller, L. Alfano, M. Iammarino, M. Moore-Clingenpeel, C. Tsao, M. Waldrop, K. Flanigan, J. Mendell, L. Lowes
Nationwide Children's Hospital, Columbus, USA

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

I. Alemdaroğlu-Gürbüz, C. İpek, Ö. Yılmaz, A. Karaduman, H. Topaloğlu
Hacettepe University, Ankara, Turkey

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

functional classification. Fear of falling (FOF) in children with DMD was assessed by ICF-Based fear of falling questionnaire for neuromuscular diseases (IBFOF-NMD) which was developed by the researchers of current study considering the characteristic features of NMD population, ICF domains, and FOF assessments in the literature. The total score ranged between 0-68 which higher scores indicate higher degrees of FOF. Physical performance was assessed by timed performance tests and 6 minute walk test (6MWT). Pediatric outcomes data collection instrument (PODCI) was used to assess quality of life. The mean score of FOF was 15.30±7.03. Positive, moderate, statistically significant correlations were determined between FOF and 10 meter walk test ($p=0.027$, $r=0.404$), ascending 4-step ($p<0.01$, $r=0.501$) while negative, moderate correlation was found between FOF and 6MWT ($p=0.015$, $r=-0.461$). There was also negative, moderate correlation between FOF and the PODCI-Global functioning ($p=0.025$, $r=-0.409$). It was determined that the children with DMD experience lower fear of falling during Daily activities which is related to physical performance and quality of life. The lower degrees of FOF may be linked to the higher number of better functioning children included in current study. The present findings suggest that even if fear of falling is not reported as a concern by ambulatory DMD children, it should be considered in physical assessments and precautions should be taken to deal with it beacuse of its relation with quality of life and physical performance.

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EP.91

The DMD-Hub, a collaboration to facilitate trials and increase trial capacity in the UK

E. Heslop [1], M. Guglieri [1], C. Turner [1], B. Crow [1], A. Peel [1], E. Crossley [2], A. Johnson [2], M. Scoto [3], F. Muntoni [3], V. Straub [1]

[1] *JWMDRC, Newcastle University, NE1 3BZ, UK;* [2] *Duchenne UK, London, UK;* [3] *UCL Great Ormond Street, London, UK*

With Duchenne muscular dystrophy (DMD) clinical research at an unprecedented stage in terms of the number of possible therapeutic approaches coming to trials, the need to increase trial capacity for DMD trials in the UK and improve trial readiness was identified. Specifically, clinicians at established UK clinical trial centres involved in multiple DMD studies were reaching capacity, while centres that did have capacity lacked the expertise and needed support to run industry-sponsored clinical trials. The DMD-Hub was set up as a partnership between UK centres of excellence and Duchenne UK. With investment exceeding 1.5 million, the DMD-Hub is facilitating the sharing of expertise and has successfully developed a network of trial-ready centres in the UK now able to take on interventional trials in DMD. To date the DMD-Hub has funded 12 additional posts at 8 trial sites in Newcastle, Liverpool, Leeds, Birmingham, Bristol and Glasgow, London and Manchester. The Hub is committed to working with further sites (including Oswestry, Cambridge and adult sites) to facilitate their involvement in upcoming industry and academic-led trials. Ongoing training for staff at sites is expected to open up additional opportunities in subsequent years. The DMD-Hub website (dmdhub.org) is a key resource for industry, clinicians and patients. It hosts an interactive map of the UK detailing clinical trial opportunities for patients, contains a repository of information and tools for sites and acts as a one-stop shop for industry / sponsors interested in conducting trials in the UK. Partnerships with industry and sites are being enabled by the DMD-Hub to facilitate trial planning, feasibility and recruitment to trials. Innovative funding models are being implemented at DMD-Hub sites to ensure sustainability. Future areas of interest for the DMD-Hub include addressing the issues related to gene therapy trials and the development of an Adult-Hub network to prepare the field for trials in the non-ambulant population. The mission of the DMD Hub is to ensure all patients with DMD, including children and adults, have access to clinical research opportunities.

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Contribution of the lower limbs in maintaining sitting balance in individuals with DMD: a pilot study

L. Peeters, M. Gameren, I. de Groot

Radboudumc, Nijmegen, Netherlands

Boys with Duchenne muscular dystrophy encounter increasing loss of muscle strength. It is known that weight support by the lower limbs is important in maintaining sitting balance when reaching forwards. Accurate positioning of the lower limbs on a supportive surface increases the base of support and thus sitting balance increases. Poor sitting balance is associated with poor functional outcome. The objective of this study is to investigate whether the contribution of the lower limbs in supporting the body weight is equal in DMD boys compared to healthy boys when performing seated arm tasks. Eleven boys with DMD and ten male healthy controls (HC) older than 8 years in comparable age range, participated in this study. The DMD participants were included if they were able to sit independently without back and arm rests for at least 10 minutes. Participants sat on a chair with a force plate mounted on top. Bodyweight was measured for 10 seconds. Next, foot support was added with knees and hips flexed in 90 degrees. Thereafter, participants performed three series of three sequential tasks: sat statically with hands resting on his legs; lifted his arms horizontally with arms tilted outwards and shoulders flexed 90°; reached forward at shoulder height when sitting upright at a distance of 140% of the arm length. Reaction forces were measured (1000 Hertz) with the force plate in three directions. The resulting force at the seat was expressed as a percentage of the total bodyweight. The percentage of bodyweight distributed through the lower limbs was defined as 100% minus contribution of percentage of the force at the seat. There was no significant difference in the contribution of the lower limbs when static sitting and lifting the arms between HC and DMD. Around 20% of the force was distributed through the lower limbs in these tasks. The contribution increased when reaching forward in both groups, however the contribution at the lower limbs was significant less ($p<0.01$) in boys with DMD compared to HC. In a former study of our group it was shown that trunk range of motion was significantly larger in DMD patients compared to HC when performing arm movements. Combined this means that sitting balance in DMD is less when performing reaching tasks. This should be taking into account in positioning of the legs while seated and in daily life activities.

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EP.93

Electrical impedance myography goes global: collaborative efforts to advance a promising preclinical and clinical tool for the development of future DMD therapies

M. van Putten [1], P. Mantuano [2], A. Aartsma-Rus [1], A. De Luca [2], M. Leitner [3], L. Dalle Pazze [4], J. Nagy [5], M. Mortreux [5], C. Semple [5], S. Rutkove [5]

[1] *Leiden University MC, Leiden, Netherlands;* [2] *University of Bari Aldo Moro, Bari, Italy;* [3] *Accelerating NeuroVentures LLC, Boston, USA;* [4] *Charley's Fund, New York, USA;* [5] *Beth Israel Deaconess MC, Boston, USA*

Improved tools to non-invasively and conveniently evaluate muscle condition and response to therapy in Duchenne muscular dystrophy (DMD) are needed. A tool with analogous application and relatable results in both preclinical and clinical contexts would be of particular interest for identifying translatable therapeutic outcomes. One approach with potential on both fronts is electrical impedance myography (EIM). EIM has been studied successfully in boys with DMD and shown correlation to functional measures, change over time, and response to corticosteroid initiation. It also can be used effectively in animal models. However, its application in mice has only been pursued by a single lab to date, impeding broader adoption and ability to relate preclinical and clinical results. In an example of cross-collaboration among industry, academic, and nonprofit partners, 3 universities, a medical device company, and patient-founded nonprofit Charley's Fund identified the opportunity to explore EIM's potential as a translatable preclinical-to-clinical tool. As an immediate next step, they developed a plan to integrate it into a 2-site,