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Analysis of the natural evolution of SV95C in ambulant patients with Duchenne muscular dystrophy

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The progressive nature of functional loss in Duchenne Muscular Dystrophy (DMD) is well established and routinely characterised in clinic using assessments such as the North Star Ambulatory Assessment and the Six Meter Walk Test. The trajectory of functional loss depends on the patient's age and baseline functional ability. There is a need to better characterise the trajectory of disease progression in order to try to predict disease evolution and optimise patient care. Stride Velocity at the 95th Centile (SV95C) is a novel clinical outcome measure that is captured during normal daily living using wearable technology and represents the maximum ambulatory ability of a patient. SV95C is qualified by the European Medicines agency (EMA) for use as a secondary endpoint in pivotal studies in DMD and is an important real-world functional endpoint complementing the traditional in-clinic assessments. SV95C declines by approximately 7% per year in ambulant patients with DMD who are on a stable dose of steroids. In other functional endpoints such as the NSAA and 6MWT the decline is dependent on the patient's age and baseline ambulatory abilities. This study aims to investigate how yearly change of SV95C is also dependent upon age and baseline function. We will analyse how the evolution of SV95C can be predicted by the baseline value of SV95C and age, using non-linear and linear multiparametric regression models. This analysis will be conducted on data from ActiLiège-NEXT, a prospective natural history study in ambulant patients with DMD. This study was designed to characterise longitudinal functional disease progression using multiple outcome measures, including SV95C. It includes patients with DMD between 4 and 20 years old studied over 1 year. SV95C was measured daily using ActiMyo®, a class I CE medical device with two sensors worn on the ankles. These data will advance our understanding of the importance of SV95C as an outcome measure for functional disease progression in DMD.

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A clinical trial simulation tool to accelerate trial design in DMD: description of the traphical user interface features and applications

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Duchenne muscular dystrophy (DMD) is a rare, fatal, X linked, muscle wasting, and progressive disease that predominantly affects boys but has been shown to manifest in some female carriers. Despite recent progress in the drug development pipeline, trial design for DMD remains difficult due to challenges intrinsic to the nature of the DMD population and the limited understanding in rate of change of endpoints in given populations. The Duchenne Regulatory Science Consortium (D-RSC) at Critical Path Institute (C-Path), has developed a model-based clinical trial simulation (CTS) platform based on a series of quantitative models of disease progression that allow researchers to design clinical trials in silico. In November 2022, D-RSC received a Letter of Support from the European Medicines Agency (EMA), and the CTS tool is currently being reviewed by the U.S. Food and Drug Administration (FDA). To allow an open and broad use of the CTS platform, D-RSC generated a web-based user-friendly graphical user interface (GUI). We describe here how to navigate the D-RSC CTS GUI for the implementation of trial design components, such as the length of follow-up, inclusion/exclusion criteria, and sample size, which may be linked to hypothesized drug effect magnitudes in an endpoint-specific fashion. Although this tool is not intended to replace functional evaluation of the assessment of efficacy in trials for DMD, the CTS tool will allow users to optimize population selection and overall trial design with flexible specification of the simulated population. Acknowledgements On behalf of the Duchenne Regulatory Science Consortium (D-RSC) and the CINRG DNHS investigators. With special thanks to PPMD, D-RSC Industry Members, Academic and Clinical Collaborators, Advisors, C-Path Staff, The Cooperative International Neuromuscular Research Group (CINRG) Investigators from the CINRG DMD Natural History Study (DNHS), ImagingDMD Investigators. This presentation is based on research using data from CureDuchenne that has been made available through Vivli, Inc. Vivli has not contributed to or approved and is not in any way responsible for the contents of this publication. ImagingDMD's data was supported by NIH grant R01AR056973.

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Six-year long-term safety and efficacy of Golodirsen in patients with DMD vs mutation-matched external controls

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Golodirsen is FDA approved for the treatment of Duchenne muscular dystrophy (DMD) in patients with exon 53 skip-amenable mutations. Results from Study 4053-101 (NCT02310906) and the open-label extension (OLE) 4045-302 (NCT03532542) evaluating the safety and efficacy of golodirsen treatment up to ~6y in patients with progressive disease deterioration are described. Post hoc analyses comparing ambulatory and pulmonary function of golodirsen-treated patients with matched (including age, mutation, steroid use) external controls (EC) were performed. Twenty-five patients received treatment at mean age 8.8y; 18/25 (72%) completed the OLE up to 6.49y. Overall, golodirsen was well tolerated: treatment-emergent adverse events were generally mild, non-serious, and unrelated to treatment; there were no treatment-related discontinuations, kidney abnormalities, or port-related infections in the OLE. At year 3, loss of ambulation (LOA) occurred in 4/25 (16%) of golodirsen-treated patients compared with 12/54 (22.2%) age- and mutation-matched EC, representing a 91.1% risk reduction (HR 0.089; P=0.0224). Over 6y, 15 golodirsen-treated patients experienced LOA (10.7–19.5y), with 7 patients still ambulant at OLE completion (12.4–20.3y). Compared with age- and mutation-matched EC (n=16), golodirsen-treated patients experienced a median delay in time to LOA of ~2.4y, representing a 47.4% risk reduction (HR 0.526, P=0.149). A separate post hoc analysis suggested that golodirsen-treated patients (≥10y) experienced a statistically significant and clinically meaningful attenuation in the annual rate of percent predicted forced vital capacity decline compared with mutation-matched EC (2.9% vs 6.67%; P<0.01). Overall, golodirsen treatment up to ~6y demonstrates a favorable, consistent safety profile and supports its long-term efficacy vs mutation-matched EC. This is the longest follow-up of safety and functional benefit of golodirsen in a declining DMD population.

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Analysis of upper limb functional outcomes in a single centre paediatric cohort of non-ambulatory patients with Duchenne muscular dystrophy

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There is limited knowledge of disease course in the nonambulatory phase of Duchenne muscular dystrophy (DMD), as well as of efficacy of glucocorticosteroid (CG) therapy in this population, in particular on upper limb function. Here we