Accelerating Drug Development for Duchenne Muscular Dystrophy: Data Sharing and Development of Quantitative Drug Development Tools Through the Duchenne Regulatory Science Consortium (D-RSC)

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Objectives: To develop a quantitative drug development tool to optimize patient enrollment, trial enrichment, stratification approaches and selection of endpoints, based on a joint disease progression model linking forced vital capacity (FVC) to clinically relevant disease milestones, built upon an integrated and standardized patient-level database of data from Duchenne clinical trials and observational studies.

Methods: The proposed joint model will link an empirical non-linear mixed-effects model that captures FVC dynamics, including relevant covariates (baseline severity, steroid use, etc.) to parametric time-to-event models for clinically-relevant endpoints (functional milestones, ambulation and airway-clearance/ventilation). This model will be developed using integrated patient-level data from clinical trials and observational studies and will be submitted for formal regulatory review via FDA’s Fit-For-Purpose Initiative, and EMA’s Qualification of Novel Methodologies in Drug Development pathway, seeking formal endorsement.

Results: The Duchenne database contains 7 integrated datasets that will soon be ready for analysis, following standardization per the Duchenne-specific Clinical Data Interchange Standards Consortium (CDISC) terminology. D-RSC’s modeling and simulation workgroup has proposed definitions of sequential disease milestones for the time-to-event analysis, which will be driven by the longitudinal FVC model, and has determined that the target milestones can be derived uniformly from the datasets.

Conclusions: Given the low prevalence and orphan status of Duchenne muscular dystrophy, a sound data-sharing structure and a rigorous data management framework is required to consolidate and catalog relevant information. By integrating patient-level data across multiple studies using CDISC standards, D-RSC has established a database that meets these criteria, and will support the development of robust, regulatory-endorsed, quantitative drug development tools. As these tools will feature models that capture clinically relevant endpoints and integrate patient-level covariates, a clinical trial simulation platform built upon these models is anticipated to improve the design of future clinical trials in patients with Duchenne.