Physical Function of Eteplirsen- and Golodirsen-Treated Duchenne Muscular Dystrophy Patients: Methodology of the Longitudinal Evaluation of Exon-Skipping–Amenable Patients (LEAP) Study

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BACKGROUND

- Duchenne muscular dystrophy (DMD) is a rare, fatal neuromuscular disease caused by mutations in the *DMD* gene, which encodes the protein dystrophin that maintains muscle cell integrity[1-3]
- Over time, deficiency of dystrophin leads to progressive muscle degeneration and weakness that results in difficulty ambulating, decline in upper limb function, cardiac performance, and respiratory strength, loss of independence in activities of daily living, and the need for use of a wheelchair by the early teen years[2-5]
- Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) that was approved by the United States Food and Drug Administration (FDA) in 2016 for the treatment of patients with *DMD* and a confirmed *DMD* gene mutation amenable to exon 51 skipping (≈13% of DMD mutations)[6,7]
- The US FDA has accepted and is reviewing a New Drug Application for golodirsen, a PMO in clinical development for the treatment of patients with DMD and a confirmed *DMD* gene mutation amenable to exon 53 skipping (≈7.7% of DMD mutations); the regulatory action date is August 19, 2019
- Novel functional assessments that capture subtle movement changes in ways that do not rely on motivational factors and that can take place in the patient's natural environment without the pressure of a formal professional evaluation, are needed to supplement clinical trial outcome measures when evaluating new treatments for DMD[8]

OBJECTIVES

- In the Longitudinal Evaluation of Exon-Skipping–Amenable Patients (LEAP) study, the secure, smartphone-compatible Caregiver Video Assessment app (Casimir Trials, LLC; Plymouth, MA) will be used alongside caregivers' observational reports of patients' functional status to achieve the following study objectives:
  - Evaluate longitudinal treatment outcomes in nonambulatory patients who have DMD and confirmed mutations amenable to exon 51 skipping and who are receiving eteplirsen
  - Evaluate progression of DMD in ambulatory and nonambulatory patients with DMD and confirmed mutations amenable to exon 53 skipping who agree to receive golodirsen upon its approval by the US FDA
- The Caregiver Video Assessment, which allows caregivers to capture the movements of DMD patients in their own homes, was developed through qualitative research with patients, caregivers, clinicians, and movement analysis experts, and is currently being validated
- These real-world data will complement standardized tests performed in the medical office or clinical trial setting, and may identify subtle, preliminary changes in muscle function that are not detected on timed tests

METHODS

Study participants

- Starting in Q2 2019 and recruiting US patients for the following 2 years, the LEAP study aims to enroll 100 patients aged ≥5 years with DMD
  - Nonambulatory patients with confirmed mutations amenable to exon 51 skipping who are taking eteplirsen (n=50)
  - Ambulatory and nonambulatory patients with confirmed mutations amenable to exon 53 skipping who agree to receive golodirsen following its approval in the US (n=50)
- Inclusion and exclusion criteria are presented in **Table 1**

Table 1. LEAP study inclusion and exclusion criteria

Inclusion Criteria	
Age, y	• ≥5 years at time of informed consent/assent
Sex	• Must be male
Disease status	• Confirmed clinical diagnosis of DMD and a confirmed out-of-frame deletion that is amenable to either: 1. Exon 51 skipping *and* patient is receiving or will receive treatment with eteplirsen and patient is nonambulatory[a] OR 2. Exon 53 skipping *and* patient is ambulatory or nonambulatory *and* patient is not currently enrolled in a clinical trial[b] • Decision to prescribe eteplirsen outside the clinical trial setting has already been made (this will also apply to golodirsen once approved by the US FDA)
Ability to participate	• Willing and able to comply with movement instructions • If aged ≥18 years, able to provide informed consent • If <18 years, a parent or legal guardian to provide informed consent, and patient to provide informed assent
Exclusion Criteria	
	• Participation in any ongoing clinical trial at time of enrollment[b] • Prior exon-skipping therapy (treatment initiation >4 weeks before enrollment) for patients amenable to exon 53 skipping

[a]Nonambulatory is defined as being unable to take steps independently.

[b]Patients who are participating in a clinical trial will become eligible for this study once they complete all clinical trial assessments and discontinue the previous trial.

- To address selection bias, the study will document all patients who decline to participate or who are excluded from participation

METHODS continued

Study materials

- At baseline, caregivers will receive training materials in the mail describing how to record the child's assigned movements using the smartphone video application (**Figure 1**)
  - Instructions include guidance on video capture (eg, how to standardize lighting, clothing, timing, and distances, and how to submit videos securely)
  - Training videos provide examples of patients performing the assigned movement activities
- Study supplies mailed to caregivers will include stickers to place on patients' hips and shoulders, a cup with a fill line, painter's tape, a tape measure, and a bed wedge
  - Supplies and assigned movement activities will differ based on each patient's functional status

STUDY END POINTS

- **Primary end points**
  - Ambulatory patients: proportion of patients with loss of ambulation (LOA) at the end of the study, based on caregiver-reported date (month, year) when loss of ability to take steps independently occurs
  - Nonambulatory patients: change from baseline in the Brooke Upper Extremity Scale grade, as determined by evaluation of videos by trained physical therapists
- **Secondary end points evaluated in eligible ambulatory patients at each assessment**
  - Percentage change from baseline in the time to rise from floor
  - Proportion of patients with time to rise from the floor of <7 and ≥7 seconds
  - Proportion of patients with loss of ability to rise from the floor, defined as inability to rise from the floor in 30 seconds without assistance or the use of furniture
  - Proportion of patients with LOA, based on caregiver-reported date for loss of ability to take steps independently
- **Secondary end points evaluated in all eligible patients at each assessment**
  - Brooke Upper Extremity Scale grade
  - Change in Brooke Upper Extremity Scale grade from baseline, as determined by physical therapist's assessment of videos
  - Physical therapist rating of quality of movement in specific movement activity video assessments, selected based on functional status

Assessments

- Caregivers will complete questions on patients' functional status using an electronic caregiver report form (CRF) at baseline and before each 6-month follow-up assessment
- Assessments of video-captured movement activities (**Table 2**) will be collected at baseline and every 6 months thereafter, using the smartphone application
  - Caregivers will use an Apple (iOS 10+) or Android (5.1+) smartphone, which will be provided if necessary
  - Assigned movement activities will change according to changes in patients' functional status

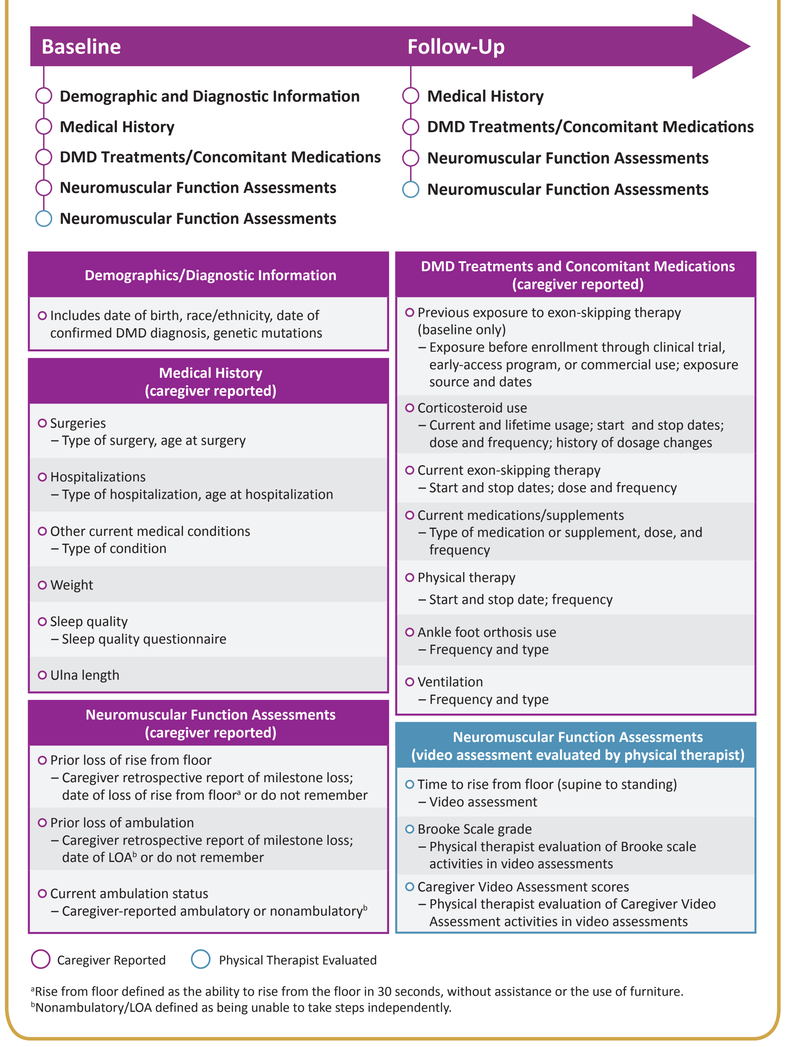
Table 2. Summary of movement activity assessments in eligible patients

Functional Status	Movement Activities
Caregiver Video Assessment	
Ambulatory patients (before loss of rise from floor)	• Climb 5 stairs • Walk/run • Jump • Sit up from supine • Supine to standing
Ambulatory patients (after loss of rise from floor)	• Climb 5 stairs • Walk • Sit up from supine • Stand up from sitting on chair
Nonambulatory patients with Brooke Scale grade 2–4	• Sit up and lean side to side in bed • Take a t-shirt off and put it back on • Eat 10 bites
Nonambulatory patients with Brooke Scale grade 5	• Take arms off wheelchair armrest and put them back on • Reach across table to grab an object • Sit up and lean side to side in bed
Nonambulatory patients with Brooke Scale grade 6	• Push a remote button • Use joystick to move power wheelchair forward
Brooke Scale Assessment	
All patients	• Raise hands above head • Raise glass of water to mouth • Raise hands to mouth • Push a remote button • Caregiver's choice of activity • New ability

Brooke Scale, Brooke Upper Extremity Scale.

- To evaluate disease progression, 2 independent physical therapists trained to identify movement changes indicating DMD progression will analyze videos to determine a severity score for each movement activity at each time point, based on the proportion of movement criteria present for each activity
  - An average of the severity scores for each movement activity will serve as the final severity score for that time point
  - Scores will be compared across time points on an additive or multiplicative scale
  - Movement assessment assignments will be updated based on changes reported in the CRF
- Adverse events will be recorded and summarized by genotype (exploratory analysis)
- Electronic CRFs and video assessments for patients already receiving eteplirsen will be collected at baseline then every 6 months; patients who start eteplirsen treatment within 4 weeks of enrollment will be followed from 3 months after baseline, then every 6 months thereafter
- All enrolled patients will be followed for 3 years from their date of study enrollment, or until withdrawal of consent or patient death
- The full data collection schedule is detailed in **Figure 1**

Figure 1: Planned data collection schedule



[a]Rise from floor defined as the ability to rise from the floor in 30 seconds, without assistance or the use of furniture.
[b]Nonambulatory/LOA defined as being unable to take steps independently.

Data analyses

- Efficacy analyses will be performed by genotype status, and safety analyses will be conducted by genotype status and for the overall population
- Continuous and categorical variables will be reported using descriptive statistics

Ethics statement

- The LEAP study will be conducted in accordance with the approved protocol, the Guidelines for Good Pharmacoepidemiology Practices, the principles of the Declaration of Helsinki, and the International Council for Harmonisation Good Clinical Practice guidelines

CURRENTLY ENROLLING

- Physicians in the US who are prescribing eteplirsen for treatment of patients with DMD aged ≥5 years, their staff, DMD advocacy groups, and DMD support groups are invited to provide eligible patients with information regarding the LEAP study

ACKNOWLEDGMENTS & DISCLOSURES

This study was sponsored by Sarepta Therapeutics, Inc. Medical writing and editorial support were provided by Peloton Advantage, LLC, an OPEN Health company, and funded by Sarepta Therapeutics, Inc.

K Tsai, Y Zheng, and O Mitelman are employees of Sarepta Therapeutics, Inc. and may own stock/options in the company. C McSherry and M Leffler are employees of Casimir Trials, LLC, which received funding from Sarepta Therapeutics, Inc. to develop the outcome measures used in this study.

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