Natural history data argues against strength and function as co-primary endpoints in Duchenne muscular dystrophy

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Two co-primary endpoints should therefore be pre-specified from the domains motor functioning and muscle strength.

New data is available which informs this issue and argues against these two co-primary endpoints.
With disease progression DMD boys walk more slowly despite minimal changes in weak focal knee extension strength (McDonald 2005)

- DMD boys walk more slowly despite minimal changes in weak focal knee extension strength (McDonald 2005)

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>DMD</th>
<th>% of Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity (6MWT)</td>
<td>103 ± 14</td>
<td>61 ± 14</td>
<td>59.2%</td>
</tr>
</tbody>
</table>
Data indicates that a different stages of disease progression in DMD either there is a large change in strength with small change in function or there is a large change in function with small change in strength.

- Data from UC Davis and the Cooperative International Neuromuscular Research Group submitted for publication
There is a logarithmic relationship between knee extension strength and 6-minute walk distance. (McDonald et al. Muscle & Nerve 2013 May 14. doi: 10.1002/mus.23905.)
Strength and Function

• The relationship between strength and function is not linear

• Loss of meaningful milestones is predicted by loss of a critical threshold of antigravity strength determined by MMT. This impacts the ability to compensate to maintain function.
Mean strength changes by myometry over 48 weeks

No significant differences in strength change over 48 weeks for corticosteroid treated versus non corticosteroid treated patients

Δ = - 1.8 lbs
Knee Ext

## Ratio of MCID / Baseline Means (PTC 007 Ataluren Trial)

<table>
<thead>
<tr>
<th>Endpoint / Statistical Method for MCID</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Correlation*</th>
<th>MCID</th>
<th>MCID / Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6MWD, m</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Error of Measurement Method (SD * √ (1 – r))</td>
<td>174</td>
<td>358</td>
<td>95</td>
<td>0.91</td>
<td>28.5 *</td>
<td>8.0%</td>
</tr>
<tr>
<td>1/3 of SD Method (SD * 1/3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31.7 *</td>
<td>8.9%</td>
</tr>
<tr>
<td><strong>Knee Extension Strength by Myometry, lbs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Error of Measurement Method (SD * √ (1 – r))</td>
<td>174</td>
<td>13.4</td>
<td>7.1</td>
<td>0.91</td>
<td>2.1</td>
<td>15.7%</td>
</tr>
<tr>
<td>1/3 of SD Method (SD * 1/3)</td>
<td></td>
<td>13.4</td>
<td>7.1</td>
<td></td>
<td>2.4</td>
<td>17.9%</td>
</tr>
</tbody>
</table>

Estimates of the MCID for 6MWD and Knee Extension strength in DMD based on pretreatment baseline data

*MCID < 48 week change

EMA Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy

• “Two co-primary endpoints should therefore be pre-specified from the domains motor functioning and muscle strength.”

• Two co-primary endpoints (not composite endpoints)

• Better not to dilute the effect on the most sensitive and meaningful primary endpoint (function) by adding a pre-specified co-primary endpoint that is not as sensitive (strength). Strength may be an appropriate secondary endpoint.
Observations –
Strength as endpoint in DMD

- Changes in strength and function vary by stage of the disease (logarithmic relationship)

- Strength may be appropriate for therapeutics leading to short-term benefit in force production of fibers.

- Strength not appropriate for clinical trials of therapeutics that stabilize functional loss without changing strength (e.g. dystrophin restoration).

- Placebo data indicate decline in strength was minimal over 48-weeks (< the MCID)

- Limitations in strength measurement:
  - Lack of normative and percent predicted values for age
  - Floor effect of lower extremity strength values typically seen in DMD patients ages 7 and older, which were low at baseline and declined minimally over 48 weeks, as seen in this study
  - Decreased reliability < age 5 is a problem
Problems with Strength and Function as co-primary endpoints

1) Function is always more important to patients and families as compared to strength;

2) Specific mechanisms of action do not lend themselves to strength and function as co-primary endpoints (e.g. dystrophin restoration);

3) Statistical power is compromised by co-primary endpoints particularly when one (function) is more responsive to therapy and more meaningful to patients than the other.