Optimal Selection of Study Population for Orphan Neuromuscular Disease Trials – A Bayesian Adaptive Approach

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Disclaimer

This presentation reflects the views of the author and should not be construed to represent Pfizer’s views.
Shares in PTC Therapeutics plunge following FDA Refuse to File letter

In retrospect, was there anything could’ve been done to avoid this?

>$500MM and >50% total market cap evaporated
Duchenne Muscular Dystrophy (DMD)

- Duchenne Muscular Dystrophy: a genetic disorder characterized by progressive muscle degeneration and weakness

- In early stages, DMD affects the muscles of shoulder, upper arm, hips and thighs, which lead to difficulty in rising from the floor, climbing stairs, maintaining balance and raising the arms

- Most patients lose ambulation during their teens

- Life expectancy: survival into early 30s become more common

- Primary endpoints used in clinical studies
  - Change in Six minute walk distance (6MWD)
  - Change in Four stairs climb time (4SCT)

Reference: The Muscular Dystrophy Association (MDA)
https://www.mda.org/disease/duchenne-muscular-dystrophy
12m Δ in 6MWD (Primary Endpoint of the Ph3 Trial)
PTC Imaging data and 6MWD

Imaging data illustrate infiltration of muscle by fat and fibrous tissue

Data courtesy of H. Lee Sweeney, Ph.D.
Myology Institute, University of Florida
Bayesian Thinking
-- Let (totality) data guide us

• Identify the Data Cloud
  - Natural history studies
  - Investigator initiated studies
  - KOLs
  - Competitor intelligence
  - Literature reviews

• Trim Data

Collecting, assembling, and quantifying data is work
-- Donald A. Berry

• Refresh data, & renew knowledge during trial

  Prior (Totality Knowledge at Present)
  × Likelihood (Emerging Experiment Data)
  ∝ Posterior & Predictive (Renewed Totality Knowledge)

Today’s Posterior Shapes  Tomorrow’s’s Prior
The Journey of a Thousand Miles Starts with a Single Step

• Step 0: data triggers (educated) curiosity

Does 6MWD baseline intervals distinguish study populations?
Natural History Data
– Sounding Board for Study Strategization

• DMD natural history data collectively seem to show that patients’ baseline functional performance is predictive of subsequent disease progression

• (As in PTC’s press release) 12m disease progression measured by 6MWD suggests 6MWD baseline might indicate 3 distinct study populations
  – 6MWD BL <300m
  – [300,400m]
  – >400m
Instrument Capability or Real Pattern?

• DMD NH data seem to suggest that the scores of functional tests like 6MWD and 4SCT at either end of the score spectrum seem to show lower signal-to-noise ratio

• Uncertain root cause:
  – Less (insufficient) samples at extremes?
  – Sub-optimal accuracy at instrument extreme scores?
  – Disease progression at relatively severe states tend to be more variable?
Bayesian Adaptive Mechanism

• Step 1: pre-specify N candidate study populations (N ≤ 4) by distinct baseline functional score intervals (and the projected progression trajectories)
  – “Totality” data:
    • Major source: well-conducted natural history study
    • Published competitor clinical trial placebo data
    • KOLs, etc

• Step 2: Construct “prior” distribution for each population
  – Variable of focus: signal-to-noise (STN) ratio, i.e. quasi-placebo effect size ratio
  – May want to use trimmed statistics to preserve robustness
Adaptation During Trial

• Step 3: Throughout course of trial, monitor placebo group and update the probability with accumulated data

\[ Prob(\text{Max}(STN_i) > \text{Min}(STN_i) | Data_T), i = 1, \ldots, N \]

Where \( i \) is the \( i^{th} \) candidate population, \( Data_T \) stands for totality data including placebo data, natural history, emerging competitor data, and also predicted data using longitudinal model.

• Step 4: stop enrollment into the group that has the lowest STN ratio as soon as

\[ Prob(\text{Max}(STN_i) > \text{Min}(STN_i) | Data_T) > P_T \]

Where \( P_T \) is pre-set probability threshold, say 80%.

• Step 5: Continue (periodically in practice) monitoring the probability and drop more groups as soon as the boundary is met.
Advantages

• Use totality data (trial data, NH, emerging competitor data, qualitative KOL input etc) to guide the search for most promising study population

• Adaptation decision criteria implemented on placebo arm only which may encounter less regulatory hurdle

• Pre-specified quantitative decision rules facilitate simulation and control of type-I error, study power & risk management
What if PTC had used this design?
Time Frame

• PTC Phase 2:
  – Study Start Date: February 2008
  – Estimated Enrollment: 174
  – Study Completion Date: December 2009

• Phase 3:
  – Study Start Date: March 2013
  – Estimated Enrollment: 220
  – Estimated Primary Completion Date: June 2015

• Phase 2 result & NH data offer natural source for eliciting sound prior

*Based on public information on www.clinicaltrials.gov*
Phase 2 Result & NH Data Form the Prior

Reference: CM McDonald et al. The 6-Minute Walk Test and Other Endpoints in Duchenne Muscular Dystrophy: Longitudinal Natural History Observations Over 48 Weeks from a Multicenter Study. Muscle and Nerve June 2013, 343-356
Prior: Knowledge before Phase 3

- Studying of NH datasets and correlations among endpoints (e.g. 6MWD & 4SCT), one can establish the prior distribution:

\[ \text{Prob}(STN_{\text{mid}} > STN_{\text{other}} | Data_T) \], where “mid” stands for the population with BL 6MWD in [300, 400m] interval, and the prior probability is approximately within [60%, 75%]

- Signals are fairly coherent across natural history datasets
Adapt & Update Prior with Trial Data

• If setting decision criterion to drop sub-optimal study populations once

\[ \text{Prob}(STN_{mid} > STN_{other} | Data_T) \geq 80\% \]

• Then simulations suggest, assuming the correlations in NH longitudinal data, enrollment of subjects with BL 6MWD <300m or >400m can be stopped once 30-45 subjects enrolled

<table>
<thead>
<tr>
<th>Baseline 6MWD (m)</th>
<th>ACT DMD N=228</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>364m</td>
</tr>
<tr>
<td>&lt; 300 m (% / n)</td>
<td>20% / 45</td>
</tr>
<tr>
<td>300 m – 400 m (% / n)</td>
<td>43% / 99</td>
</tr>
<tr>
<td>&gt; 400 m (% / n)</td>
<td>37% / 84</td>
</tr>
</tbody>
</table>
Ph3 Trial Result, had this Design Used

Positive Trial Result -- Primary Endpoint is Statistically Significant

>30 m (p < 0.02)

Due to lack of access to subject-level data, the results with actual data may vary
More Effective?

• What if the adaptation start since Ph2 and install seamless Ph2 & 3 design?

• NH data alone can formulate sound prior

• Inferentially seamless or operationally seamless?

• Likely to cut down development time and cost further & harvest higher probability of trial success
Out of intense complexities, intense simplicities emerge.

- Sir Winston Churchill