Optimizing Clinical Trial Design in Rare Progressive Disease

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GNE Myopathy

- Rare genetic muscle disease
- Slowly progressive muscle weakness and atrophy effecting different muscle groups at different stages of the disease
- *Goal: Does the treatment slow decline of muscle strength?*
Familial Frontotemporal dementia (fFTD)

- Some forms have a genetic cause (10-20% all FTD)
- Resulting from progressive degeneration of the temporal and frontal lobes of the brain
- Results in behavioral, language and/or motor symptoms
- Age of onset between 30-60 depending on genetic mutation
Dominantly Inherited Alzheimer’s (DIAN)

- Rare genetic form of Alzheimer’s (<1% of total Alzheimer’s population)
- Early age of onset: 30-50
- Goal: Does the treatment slow cognitive progression?
Complexities in Designing Clinical Trials in Rare Progressive Disease

• Heterogeneity in progression
• Large variability in key clinical endpoints
• Different endpoints are affected at different stages of the disease
• *Common Solutions:*
  • Enroll a more homogenous subset
  • Enroll a large enough sample size to overcome heterogeneity
  • *Both not ideal in a rare disease setting!*
Solutions for Rare Disease

GNE Myopathy
- Natural History Study -> Disease Progression Model
- Joint Disease Modification Analysis incorporating all muscle groups

DIAN
- Natural History Study -> Disease Progression Model
- Disease Modification Analysis
- Adaptive Platform Trial with freq. interims and shared Controls

FTD
- Natural History Study -> Disease Progression Model
- Disease Modification Analysis
- Adaptive Platform Trial with freq. interims and shared Controls

- Natural History Studies + Disease Progression Models -- Know what you are working with!
- Innovative Designs
  - More powerful analysis methods
  - Adaptive designs with frequent interims
  - Use all available data
Natural History Studies + Disease Progression Modeling
GNE Natural History Data
(data collected before April 1st 2016 and publication)

• **Sample Size: 38** Patients

• **Visits:** Every 3-6 months
  - Average follow-up of 14 months
  - Number of months from baseline per patient ranges from 0-38

• **Examples of Measurements taken:**
  - 6MWT: 6-minute walk test
  - AMAT: Adult Myopathy Assessment Tool
  - HAP: Human Activity Profile
  - IBMFRS: Inclusion Body Myositis Functional Rating Scale
  - QMA: Quantitative Muscle Assessment for multiple muscle groups
Possible Primary Endpoint: 6MWT

Raw Scores

Change from Baseline + Model Fit

<table>
<thead>
<tr>
<th>Change (SD):</th>
<th>1 Year</th>
<th>2 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>raw</td>
<td>-10.69 (32.69)</td>
<td>-21.38 (32.69)</td>
</tr>
<tr>
<td>N 80% Power:</td>
<td>1178</td>
<td>296</td>
</tr>
<tr>
<td>Power N=80:</td>
<td>0.11</td>
<td>0.3</td>
</tr>
</tbody>
</table>
Possible Primary Endpoint: Upper Extremity QMA Composite Subset*

Raw Scores

Change from Baseline + Model Fit

Natural Progression ± 1SD
50% Reduction in Decline
100% Reduction in Decline

Change (SD): Im
raw
1 Year
-5.66 (10.9)
-7.5
-4.88
-5.66 (10.9)
120
Power N=80:
0.21
0.63
Ultragenyx Announces Top-Line Results from Phase 3 Study of Ace-ER in GNE Myopathy

Study did not meet its primary endpoint

NOVATO, Calif., Aug. 22, 2017 (GLOBE NEWSWIRE) -- Ultragenyx Pharmaceutical Inc. (NASDAQ:RARE), a biopharmaceutical company focused on the development of novel products for rare and ultra-rare diseases, today announced that a Phase 3 study evaluating aceneuramic acid extended release (Ace-ER) in patients with GNE Myopathy (GNEM) did not achieve its primary endpoint of demonstrating a statistically significant difference in the upper extremity muscle strength composite score compared to placebo. The study also did not meet its key secondary endpoints. Adverse events were generally balanced between Ace-ER and placebo and safety was consistent with previously released Ace-ER data. Ultragenyx plans to discontinue further clinical development of Ace-ER.

"We are disappointed by these results, as we had hoped that Ace-ER would offer a new option for GNEM patients. We would like to thank the patients, caregivers, and investigators involved in the Ace-ER development program," said Emil D. Kakkis, M.D., Ph.D., Chief Executive Officer and President of Ultragenyx. "This outcome does not affect our overall strategy, as the company moves forward with multiple preclinical and clinical programs and regulatory filings."

The Phase 3 Ace-ER study enrolled 89 adults with GNEM able to walk > 200 meters in the six minute walk test. Patients were randomized 1:1 to Ace-ER at a dose of 6g/day or placebo for 48 weeks. The study did not meet the primary endpoint of demonstrating a statistically significant improvement in UEC score (+0.74 kg, p=0.5387) for Ace-ER treated patients (n=45, -2.25 kg) compared to placebo (n=43, -2.99 kg) patients for the change from baseline to 48 weeks. There were three pre-specified key secondary endpoints, including the lower extremity muscle strength composite score as measured by hand-held dynamometry (HHD), physical functioning using the Mobility domain of the GNE Myopathy-functional activity scale (GNEM-FAS), and a measure of muscle strength in knee extensors. The study did not meet any of these key secondary endpoints.
## Summary of GNE endpoints

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>1-year decline Mean (SD)</th>
<th>Sample size 2 Year Trial (80% power; 50% Reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite total strength (%predicted)</strong></td>
<td>-2.01 (5.66)</td>
<td>252</td>
</tr>
<tr>
<td><strong>Composite UE strength (% predicted)</strong></td>
<td>-1.67 (5.28)</td>
<td>318</td>
</tr>
<tr>
<td><strong>Composite LE strength (% predicted)</strong></td>
<td>-2.28 (6.85)</td>
<td>288</td>
</tr>
<tr>
<td><strong>Composite UE strength (kg)</strong></td>
<td>-4.52 (10.2)</td>
<td>164</td>
</tr>
<tr>
<td>subset 6MWT &gt;200m3</td>
<td>-5.66 (10.9)</td>
<td>120</td>
</tr>
<tr>
<td><strong>Composite LE strength (kg)</strong></td>
<td>-9.55 (20.6)</td>
<td>150</td>
</tr>
<tr>
<td>subset 6MWT &gt;200m3</td>
<td>-11.4 (20.72)</td>
<td>106</td>
</tr>
<tr>
<td><strong>6MWT (meters)</strong></td>
<td>-10.7 (32.7)</td>
<td>296</td>
</tr>
<tr>
<td><strong>AMAT total score</strong></td>
<td>-1.47 (2.52)</td>
<td>96</td>
</tr>
<tr>
<td><strong>HAP adjusted activity score</strong></td>
<td>-1.11 (5.52)</td>
<td>778</td>
</tr>
<tr>
<td><strong>HAP maximum activity score</strong></td>
<td>-3.24 (7.96)</td>
<td>192</td>
</tr>
<tr>
<td><strong>IBMFRS total score</strong></td>
<td>-0.49 (1.65)</td>
<td>352</td>
</tr>
</tbody>
</table>
Summary of exploring individual GNE endpoints

• No single endpoint provided the sensitivity needed to run a feasible clinical trial
• QMA determined to be the most direct measure of disease progression
• Goals – better understand QMA and how it each muscle progresses over the course of the disease
Disease Progression Models

• Mathematical function
• Quantitatively captures individual disease evolution
• Single or multiple disease-specific biomarkers and/or clinical outcome measures
• Likely monotonic in progressive disease
• Ideally measures are modeled as a function of disease stage <- likely unobserved
Uses Disease progression Models

• Understanding rates of progression and variability for potential clinical trial endpoints
• Evidence based clinical trial simulations
• Predict future progression given participants disease stage
  • Optimize clinical trial enrollment
  • Enable more powerful analysis methods
## QMA Measurements

<table>
<thead>
<tr>
<th>Muscle Group</th>
<th>Measured Strength (kg)</th>
<th>Percent Predicted*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upper Extremities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Grip</td>
<td>39.46</td>
<td>83.11%</td>
</tr>
<tr>
<td>R Grip</td>
<td>45.93</td>
<td>91.41%</td>
</tr>
<tr>
<td>L Wrist Ext</td>
<td>11.97</td>
<td>80.15%</td>
</tr>
<tr>
<td>R Wrist Ext</td>
<td>16.91</td>
<td>105.91%</td>
</tr>
<tr>
<td>L Shoulder Abd</td>
<td>21.50</td>
<td>88.53%</td>
</tr>
<tr>
<td>R Shoulder Abd</td>
<td>20.24</td>
<td>73.22%</td>
</tr>
<tr>
<td>L Elbow Flex</td>
<td>20.60</td>
<td>71.11%</td>
</tr>
<tr>
<td>R Elbow Flex</td>
<td>22.64</td>
<td>69.08%</td>
</tr>
<tr>
<td>L Elbow Ext</td>
<td>10.72</td>
<td>47.54%</td>
</tr>
<tr>
<td>R Elbow Ext</td>
<td>11.89</td>
<td>51.20%</td>
</tr>
<tr>
<td><strong>Sum Upper</strong></td>
<td>221.84</td>
<td>77.02%</td>
</tr>
<tr>
<td><strong>Lower Extremities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Dorsiflex</td>
<td>8.02</td>
<td>25.83%</td>
</tr>
<tr>
<td>R Dorsiflex</td>
<td>7.42</td>
<td>23.98%</td>
</tr>
<tr>
<td>L Hip Abd</td>
<td>27.48</td>
<td>77.38%</td>
</tr>
<tr>
<td>R Hip Abd</td>
<td>31.27</td>
<td>90.44%</td>
</tr>
<tr>
<td>L Hip Ext</td>
<td>56.40</td>
<td>117.54%</td>
</tr>
<tr>
<td>R Hip Ext</td>
<td>54.28</td>
<td>114.39%</td>
</tr>
<tr>
<td>L Knee Ext</td>
<td>31.49</td>
<td>53.07%</td>
</tr>
<tr>
<td>R Knee Ext</td>
<td>39.02</td>
<td>64.09%</td>
</tr>
<tr>
<td>L Knee Flex</td>
<td>23.35</td>
<td>81.94%</td>
</tr>
<tr>
<td>R Knee Flex</td>
<td>22.13</td>
<td>74.91%</td>
</tr>
<tr>
<td><strong>Sum Lower</strong></td>
<td>300.83</td>
<td>74.15%</td>
</tr>
<tr>
<td><strong>Sum Strength</strong></td>
<td>522.66</td>
<td>75.34%</td>
</tr>
</tbody>
</table>

* Based on age, gender and BMI
QMA: Natural History
GNE Disease Progression Model

• Each patient’s data is a piece of the puzzle; a small snapshot of the disease

• Unknown where a patient is in the disease course; where does the puzzle piece fit?
GNE Disease Progression Model

- Each patient’s data is a piece of the puzzle; a small snapshot of the disease
- Unknown where a patient is in the disease course; where does the puzzle piece fit?
- **All pieces together provide picture of overall progression**
Expected
Muscle Decline vs. Disease Age
**Overall Disease Summaries**

**Disease Age 0:**
- Intermittent use of handrail when climbing stairs
- Mild unsteadiness when walking
- Use substitute motions when standing from sitting
- 6MWT: ~450 meters
- AMAT high functional group

**Disease Age 10:**
- Dependent on a handrail when climbing stairs
- Intermittent use of a device for walking
- Slow turning in bed, cutting food and handling eating utensils
- Increased effort with hygiene and dressing
- 6MWT: ~340 meters
- AMAT moderate functional group

**Disease Age 20:**
- Requires use of arms when standing from sitting
- Slow fine motor tasks
- 6MWT: ~230 meters, but several patients unable to complete
- AMAT low functional group

**Disease Age 30:**
- Requires handrail and additional support to climb stairs
- Dependent on device to walk
- Great difficulty turning in bed
- Needs help with fine motor tasks, cutting food & handling utensils
- Modified technique for hygiene and dressing
- 6MWT: Not able to complete
Clinical Trial Design + Analysis Innovations
GNE DPM: Clinical Trial Simulation

- Understand operating characteristics of proposed design / analysis method
- Optimize design/analysis under key trial parameters
- Understand robustness of results to modeling assumptions
GNE DPM: Clinical Trial Simulation

Clinical Disease Progression
Knee Flex

Muscle Strength

Disease Age

0.0
0.2
0.4
0.6
0.8
1.0

-10
-5
0
5
10
15
20
Clinical Disease Progression
Knee Flex

Subject 1:
Subject-level random effect: 1.2
Years since onset at enrollment: 0
Enrolled to treatment group
GNE DPM: Clinical Trial Simulation

- N=51 Enrolled 2:1 Treatment vs. Control
- 2-year follow-up
- Treatment effects: 50% slowing in progression

Power

Alternate Single Endpoints / Analyses

10-40%
GNE DPM: Powerful Analysis tool

• Use GNE DPM to enable more powerful primary analysis tools
GNE DPM: Powerful Analysis tool

- Use GNE DPM to enable more powerful primary analysis tools
  - Reduce unexplained variability in rates of progression due to estimated disease stage
GNE DPM: Powerful Analysis tool

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  - Reduce unexplained variability in rates of progression due to estimated disease stage
  - Increase ability to differentiate variability in natural progression vs. treatment-related disease modification
GNE DPM: Powerful Analysis tool

- Use GNE DPM to enable more powerful primary analysis tools
  - Reduce unexplained variability in rates of progression due to estimated disease stage
  - Increase ability to differentiate variability in natural progression vs. treatment-related disease modification
  - Model multiple muscles jointly – all participants at all stages to inform inference
GNE DPM: Powerful Analysis tool

- Incorporate all muscles in the estimation of treatment effect (constant % slowing in disease)
- Adjust for disease stage
- Muscle where we can best detect treatment effect is subject-specific
  - Given the patients disease age, which muscle is actively decaying
GNE DPM: Clinical Trial Simulation + Powerful Analysis tool

- N=51 Enrolled 2:1 Treatment vs. Control
- 2-year follow-up
- Treatment effects: 50% slowing in progression
- **Primary Endpoint + Analysis:** Joint Disease Modification Analysis with QMA
Summary / General Advice

• Natural History Studies + Clinical Trial Simulation = More Informed Trial Design!
  • Original GNE Power = < 40%

• Use all available data
  • Innovative analysis method efficiently uses multiple endpoints, all follow-up and adjusts for disease age
  • Innovative DPMA leads to increase in power from <40% to > 80%!

• Speak with partners early and often regarding innovative design – important that all parties are comfortable with the novel approach

• Natural history / Historical patient-level databases + Clinical trial simulation is the key to understanding + getting approval of novel / complex approaches

• Invest in innovation – it may take more time / resource upfront but will lead to a more efficient and powerful clinical trial
References


