C-Path Capabilities

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C-Path Successes

Data Science:
• Demonstrated experience in data sharing, management, standardization, curation, maintenance and security

Quantitative Science:
• Demonstrated track record in model-informed drug development, including biomarkers and outcome measures

Regulatory Science:
• Demonstrated impact in the transformation of the drug development process through strategic regulatory strategy
• **Baseline Total Kidney Volume (TKV)** is an independent, statistically significant and clinically relevant predictor of kidney function decline.

• **The joint TKV-kidney-function model** accounts for all captured relevant sources of variability together.

Clinical Trial Planning Example
30% Worsening of eGFR

<table>
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<tr>
<th>Age</th>
<th>TKV</th>
<th>Follow-Up Period</th>
<th>1-Probability of 30% Worsening of eGFR</th>
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<tr>
<td></td>
<td>Baseline</td>
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<td>Median</td>
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<tr>
<td>Baseline</td>
<td>TKV 1.7L</td>
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Optimizing patient selection in early motor PD

Average monthly progression in the harmonized score (point/month):

- SWEDD = 0.05 (90% CI: -0.04, 0.13)
- DAT-deficient = 0.18 (90% CI: 0.14, 0.21)
- Difference = -0.13 (90% CI: -0.23, -0.04), one-tailed $P$-value=0.01

Average difference in the change from baseline of motor scores at 24 months between SWEDD and DAT-deficient subjects (points):

- -3.16 (90% CI: -0.96, -5.42)

DAT Enrichment allows ~24% Reduction of Trial Size to detect a Disease-modifying Drug Effect with 80% Power

Under these assumptions:
- 24-month placebo-controlled trials.
- Enriched trials had only subjects with DAT deficit, while non-enriched trials included 15% of SWEDD.
- Disease-modifying drug effect of 50% reduction in the progression rate.
- Power was calculated as the proportion of trials for which the parameter estimate for the interaction between time and treatment showed a beneficial drug effect with a two-tailed $P$-value < 0.05.

Understanding the entire disease continuum: Duchenne Muscular Dystrophy

Intent is to develop a quantitative drug development tool that describes the following:

**Longitudinal FVC Model**
- Covariates of interest:
  - Anthropomorphic measures
  - Baseline severity
  - Steroid use

**Parametric TTE models**
- Clinically Relevant Endpoints:
  - Functional milestones
  - Ambulation milestones
  - Respiratory milestones
Duchenne Disease Progression Model

Preliminary results

FVC vs. Age across all studies

- Forced Vital Capacity (L)
- Age (Years) at FVC measurement

flag
- >=7 years old
- <7 years old
C-Path Successes

Pre-defined cutoff points:

• Not needed if full distribution of quantitative biomarker is modeled as a continuous covariate.

Cutoff definition:

• Can be done in a trial-specific manner, based on simulations, given a robust quantitative understanding of disease progression.

Advantage:

• Optimized efficiency for the specific context of a given drug development program.
So...

\[ S = f(t, p) \]
Thank You