When a Threshold Crossing approach may and may not be appropriate: A Case Study in SMA

EFSP1 Regulatory Statistics Workshop, 24-25th September 2018
Carol Reid and Uli Burger
Outline

• Introduction to Spinal Muscular Atrophy (SMA)

• Designing a Study for Patients with Type 1 SMA
  – Threshold Crossing Approach
  – Primary Endpoint
  – Secondary Endpoints

• Designing a Study for Patients with Type 2 & 3 SMA

• Conclusions
Introduction to Spinal Muscular Atrophy (SMA)

- Genetic, progressive motor neurone disease characterized by muscle atrophy and weakness
- Continuous spectrum of symptoms
  - Patients classified into types according to highest level of function achieved

<table>
<thead>
<tr>
<th>Type</th>
<th>Severity</th>
<th>Age of onset</th>
<th>Typical symptoms</th>
<th>Lifespan</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Severe</td>
<td>0-6 months</td>
<td>• Never sit</td>
<td>&lt; 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Respiratory failure</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Intermediate</td>
<td>7-18 months</td>
<td>• Sit, never stand</td>
<td>&gt; 2 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Respiratory complications likely</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Wheelchair-bound</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Mild</td>
<td>&gt; 18 months</td>
<td>• Walk at least once in lifetime</td>
<td>Adult</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Muscle weakness</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Mildest</td>
<td>2nd and 3rd decade</td>
<td>• Gradual weakening of muscles in adulthood</td>
<td>Adult</td>
</tr>
</tbody>
</table>

- First treatment for SMA approved in Dec 2016 (FDA), 2017 (EMA)
Designing a Study for Type 1 SMA

- Rare disease with no approved treatments
- Study in rapidly declining infants with short life expectancy
  - Placebo control ethical?
  - Strong push from patient groups against randomized trials
- Patient population clearly defined: Genetic confirmation of SMA + clinical symptoms
- Natural history of the disease is well defined
  - Type 1 SMA infants never achieve the motor milestone of sitting
- Primary endpoint: Proportion of infants sitting without support at 12 months of treatment
  - Video-recorded and centrally assessed by 2 independent raters
  - Objective & clinically meaningful.
- Single arm study selected
  Threshold crossing approach to assess success
Threshold Crossing (Eichler et al. 2016)

• Upfront definition of an appropriate estimand defining
  – The treatment-eligible population
  – The variable of interest
  – The measure of intervention effect

• Counterfactual determined from existing RWD and/or past RCT data

• Efficacy threshold clearly higher (high bar) than the estimate of the counterfactual is set and agreed by relevant decision-makers alongside a detailed study protocol and analysis plan

• Patients who meet the predefined treatment eligibility criteria are enrolled in a single arm study

• If the threshold is crossed, efficacy is judged to be established
  – A negative result would lead to an additional study or termination of product development
Primary Endpoint Threshold & Analysis

- Type 1 infants never sit
- Threshold to be statistically differentiated set at 5%
- Hypothesis to be tested is proportion of infants who sit at month 12 (p)
  \[ \text{Ho: } p \leq 5\% \text{ vs Ha: } p > 5\% \]
- Tested using exact binomial test
  - Reject Ho if one sided p-value \( \leq 5\% \)
  - Study will be positive if lower limit of two-sided 90\% Clopper-Pearson (Exact) confidence interval is above the threshold of 5\% set for the primary objective
- Note study will be positive as soon as minimal number of infants sitting needed to achieve positive test is observed
- Study will continue for an unbiased estimate of the primary endpoint and for the assessment of secondary endpoints
Secondary Endpoints

- Secondary endpoints included to assess progression of other important aspects of the disease

- Secondary Endpoints include:
  - The proportion of infants who achieve >40 in the CHOP-INTEND
    - 16-item scale measuring motor function (hand-grasping, rolling, head control etc)
  - The proportion of infants who achieve motor milestones (head control, rolling, sitting, standing, walking)
  - Time to death or permanent ventilation

- Natural History is less well-defined
  - Can be variable and dependent on individual clinician practice & family preference
  - Mortality is generally dependent on the aggressiveness of pulmonary intervention

- Where possible, secondary endpoints will be assessed against pre-defined thresholds determined from observational and clinical trial data

- As a sensitivity analysis secondary endpoints will be compared with data from a retrospective chart-review study conducted at the same sites as the pivotal study
Thresholds for Secondary Endpoints

• Determined from similar cohorts of patients constructed from RWD sources and clinical trial data (literature search and databases)
  – All data sources and reasons for exclusion are documented in an appendix to the SAP
• Where patient level data available, summary data generated from patients with similar exclusion/exclusion criteria when possible
• Where only summary data available point estimates and confidence intervals extracted or derived
• When multiple sources of data existed for the endpoint, the cohort with baseline characteristics most similar to the targeted study population were selected
• High bar: Threshold is based on the upper limit of the 90% confidence interval (CI) derived from the historical data
• Thresholds were pre-defined in the SAP prior to study start
• Any new external data will also be presented and may be used for sensitivity analysis
Chart Review Study

- A retrospective chart-review study aims to provide additional data on the natural history of selected secondary endpoints to provide further context for the results.

- Infants with the same key inclusion criteria as the pivotal study and matched on key prognostic factors.

- Data extraction in the same centres to minimize any centre effects resulting from differences in standard of care.

- Start date selected to ensure that the standard of care for infants included is as comparable as possible to current practice.

- End date selected to eliminate the risk of over-representing infants ineligible for clinical trials and of informative censoring.

- Selection of the most recent eligible chart during the study period to further minimize the impact of any temporal trends in patient outcomes.

- Well-defined, deterministic, chart-selection process to eliminate the risk of inappropriate selection of charts.
## Study Design for Type 2 and 3 SMA

<table>
<thead>
<tr>
<th>Type</th>
<th>Severity</th>
<th>Age of onset</th>
<th>Typical symptoms</th>
<th>Lifespan</th>
</tr>
</thead>
</table>
| II   | Intermediate | 7-18 months  | • Sit, never stand  
• Respiratory complications likely  
• Wheelchair-bound | > 2 years |
| III  | Mild     | > 18 months  | • Walk at least once in lifetime  
• Muscle weakness | Normal |

Primary Endpoints focus on **motor function:**

**E.g. Motor Function Measure (MFM-32)**

- 32-item scale administered by physiotherapists that evaluates physical function in 3 dimensions:
  - standing and transfer, axial and proximal function, distal motor function
  - Items scored from 0 (unable) to 3 (fully able)
  - Objective Scale (limited scope for subjectivity)
Single Arm or Randomised Controlled Trial?

- Again clear patient preference against randomized trials but still possible to recruit patients into a placebo-controlled trial.

- Natural history of the disease is less well understood:
  - Patients decline but at variable rates depending on age and other (unknown) factors.
  - E.g. Patients aged around 5-15 decline at a greater rate than older patients.

- Smaller effects relevant: Small changes (or stabilisation) are meaningful to patients:
  - Markedly different changes less likely in older patients.

- Possible to set a threshold for success:
  - E.g. Lower 95% CI > 0 in a population expected to decline.

- May need a longer and/or larger study to be conclusive. Differentiation of smaller and medium size effects is difficult.

- Primary endpoint may have some assessment bias.
Conclusions

• In Type 1 SMA a single arm study assessed using a threshold crossing approach is appropriate
  – High ethical demand
  – Selected primary endpoint is objective with little assessment bias, clinically meaningful with
    known natural history. High bar versus natural history
  – Thresholds for some secondary endpoints determined from available natural history and clinical
    trial data are less clearly defined but still provide useful supportive information
  – Additional information from a chart review study provides supportive data from the same sites for
    sensitivity analyses

• In type 2/3 SMA a randomized study is more appropriate
  – Potential primary endpoints have limited scope for assessment bias
  – Natural history is less well-defined
  – Smaller effects may be clinically meaningful but cannot be differentiated versus natural history
  – Non-controlled study may need to be larger and/or longer to be convincing, with a potentially
    unrealistically high bar
Doing now what patients need next