Types 2 and 3 SMA: Industry Perspective

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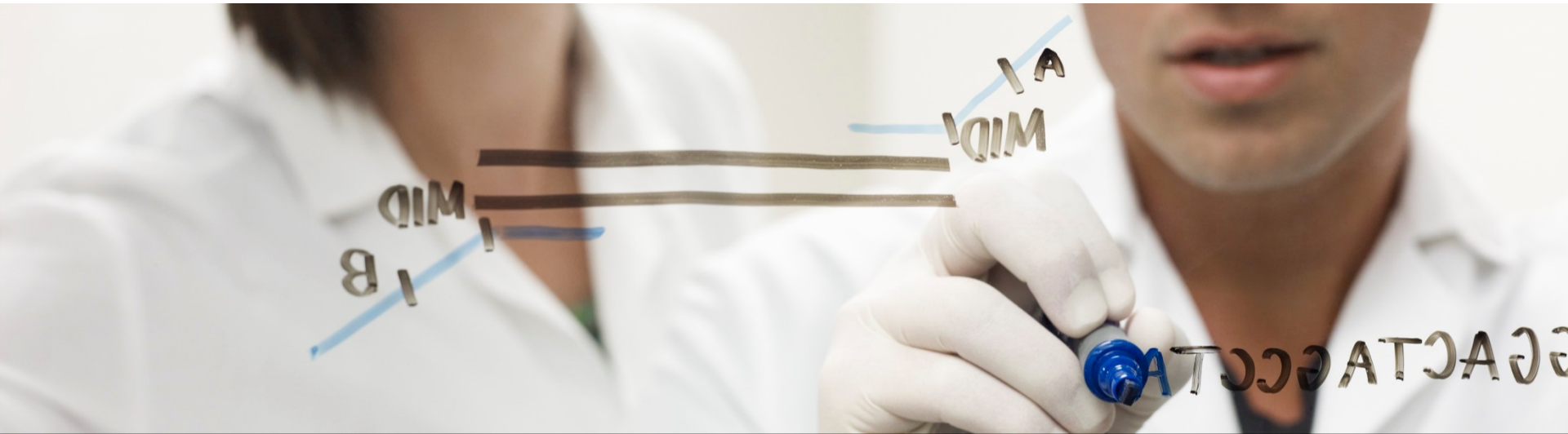

Outline

- Patient population for inclusion in trials
- Control group
- Outcome measures
- Biomarkers
- Patient Reported Outcomes
- Challenges

Patient population

Needs of the **broad SMA patient population**

Heterogeneity

Age and Body Size/Weight

Function

Disability

Comorbidities

Key drivers for patient selection

- **Target product profile**
  - Indication (age range and type/s of SMA)
  - Key claims for label
- **Pharmacokinetics of molecule**
- **Route of administration/delivery**
- **Non-clinical safety profile**
- **Toxicology coverage**
- Feasibility of assessments
- Comorbidities

Control group

- Existence of clinical equipoise
- **Number of studies and rigorous design to support registration**
- Randomization
- Configuration of randomization
- Historical or non-concurrent controls
- Pooling of control data
- Power and sample size
- Feasibility of recruitment within timelines

Outcome measures I

- Selection of primary, key secondary EP, secondary EPs, exploratory EPs
  - Co-primary, composites, **preservation of statistical power**
  - **Measurement properties**
  - **Clinical Meaningfulness and MCID**
- **Sample size and power considerations**
- **Duration to see effect**
- **Applicability** across
  - age range
  - ambulation status
  - disability
  - orthopedic status

Outcome measures II

- Lower extremity, axial/trunk and upper extremity function
  - **Optimum measure/s**
- **Pulmonary function testing**
- **Assessment of comorbidities**
- **Disability/ability** status
- Integration of **Real World Evidence**

Biomarkers

- **Intended use** of biomarker
  - Target engagement and PKPD analysis
  - Efficacy or surrogate endpoint
  - Safety
- **Robustness** of assay (reliability, stability, reproducibility)
- Fluid and tissue biomarkers (blood, CSF: mRNA, SMN protein, other)
- Electrophysiological measures (CMAP, MUNE)
- Digital biomarkers (sensors, wearables)

Patient Reported Outcomes

- **Pediatric PROs**
- Meet needs of range of patients
- Instruments to meet **Health Technology Assessors needs**
- Patient versus caregiver, physician or other proxy
- Concept of “burden”
- Robustness of evidence to support PRO
- Health-related QoL, QoL
- **Independence, ability and disability status**

Challenges

- **Epidemiology of Types 2-4**
- **Extrapolation** across age, disease type and ambulatory status
- **Recruitment**
- **Establishment of clinical meaningfulness**
- Requirement for placebo group and when does equipoise no longer exist?
- Availability of robust control and **natural history data**
- Duration of treatment
- 8 month to 2 year olds
- Comparator and **combination studies**
- *Pre-symptomatic patients*

Doing now what patients need next