EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Ambulant & non ambulant (Types 2 & 3) Spinal Muscular Atrophy

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SMA EMA workshop

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Content

Relevant SMA characteristics

Population

Assessment of treatment effect

Study design

Other issues

What can EMA offer?

Spinal Muscular Atrophy – Relevant aspects

Predominantly Neuromuscular Disorder

- Continuum of clinical presentation

- Motor milestones achieved up to a certain level, then decreasing progressively

  Under treatment

  – Cinical stabilisation / improvement /worsening as variables
- Different genetic forms / SMN copies
  – Patient population refinement
- Progression speed
  – study duration timeframe

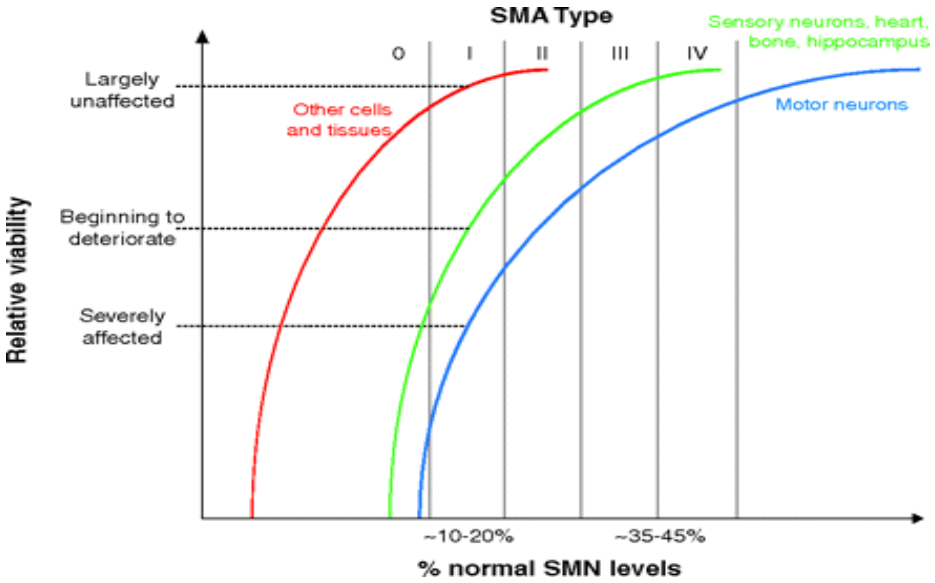
Pathophysiology

Direct

- Motor spinal neurons impairment
- Other tissues involvement (Skin?)

Indirect

- Dysphagia - wasting
- Skeletal dysmorphia
- Respiratory failure
- Infections



The contribution of mouse models to understanding the pathogenesis of spinal muscular atrophy
Sleigh J et al. Disease Models & Mechanisms 2011 4: 457-467.

Population

Trial population / Extrapolation

- SMA 1 vs SMA 2 vs SMA3;
- SMA 1 vs other SMA
- SMA early onset vs late onset SMA (cut off at 6Mths?)

Ambulant vs non ambulant (at time of screening)

Literate vs preschool patient

SMN2: 2 copies vs 3 copies vs 4 copies

Severe clinical status vs moderate clinical status (at time of screening)

Pre-symptomatics

Pre-symptomatic patients

Importance in late onset SMA

Genetic testing in pre-symptomatic children

- ethical / legal issues if no approved therapy available

SMN2 copies

CMAP / MUNE neurophysiology

...

Assessment of treatment effect in SMA types 2 & 3

Matching

- Disease severity (non ambulant / ambulant)

- Learning abilities (infants / children / adolescents) – test performance
  - More complex than SMA type 1

- Tool features
  - Discriminative power
  - Floor effect
  - Ceiling effect

Assessment of treatment effect in SMA types 2 & 3

Tools needed for:

- Motor function (pyramidal tract)
  - MFM 32 vs 20; MFM total vs D1+D2 domain
  - HFMSE (sitting, non ambulant patients)
  - 6MWT (fatigue)
- Respiratory function
  - Time to ventilation
    - Non invasive? (16 hours per day?) Invasive?
  - FVC
- Global Function
  - CGI
  - PGI?
- Common morbidities
  - Age limits to control for scoliosis / respiratory
- ADL / Learning abilities
- QoL
  - PedsQL
- Caregiver burden
- Pharmacoeconomic endpoints

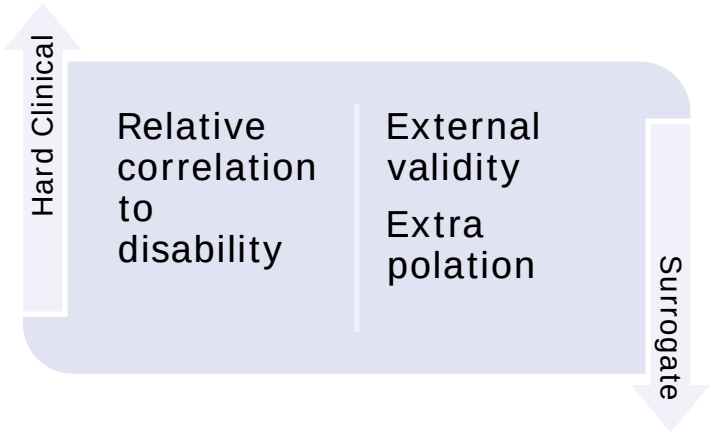
Potential surrogate endpoints

Motor neuron related

- SMN transcript and/or protein
- CMAP, MUNE, EIM
- …

❖ Unable to measure influence of comorbidities

❖ Not a global assessment tool



Study design

Comparator

- Placebo
  - Valproate

    Rak K et al, Neurobiol Dis. 2009 Dec;36(3):477-87.

    Treating agent may also be deleterious
  - Best medical treatment inhomogeneity among study centres
- Historical comparator
  - Best medical treatment
    - evolution
  - Earlier diagnosis – treatment support

Mapping the differences in care for 5000 Spinal Muscular Atrophy patients, a survey of 23 national registries in North America, Australasia and Europe.

Bladen, C.L, The TREAT-NMD SMA Group and Lochmuller, H.
MRC Centre for Neuromuscular Diseases at Newcastle Institute of Genetic Medicine
Newcastle University International Centre for Life
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TREAT-NMD Neuromuscular Network

Study design

Comparator

- New approval scenario
  - Use of placebo vs newly approved agent
    - Different indication
    - Demonstration of superiority
  - Significant benefit

Study design

Adaptive design

Vs

Exploratory ↗ Confirmatory design

Regulatory requirements at MA:

- Post approval registries
- Post Approval efficacy studies
- Post Approval Safety Studies

Other issues

Study duration

Study enrolment and stopping rules

Cut-off points:

- a) when to start treatment
  - some already highly disabled infants do not improve and treatment might just prolong time to ictus, with no benefit
- b) when to stop treatment
  - lack of treatment effect – definition of responder

HTA assessment facilitation

Market Authorisation is different from treatment access

How to prepare for HTA

- Natural history cohorts
- Pharmacoeconomic friendly endpoints
- Duration of treatment estimate

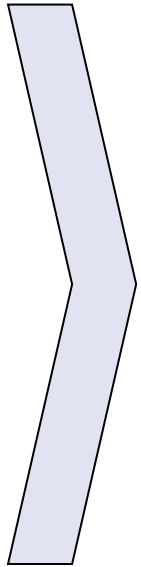
What can EMA offer?

Early access for scientific advice and protocol assistance

- All development phases (SA and PA);
- Selection / recommendation on specific assessment tools (Qualification Advice and Qualification Opinion)
- PRIME

Early access to the market
(Conditional Marketing Authorisation)

Speeded procedures
(Accelerated Assessment for MA)



PRIME:
priority medicines

Fostering early dialogue among stakeholders

- Patients
- Drug developers
- Investigators / Clinicians
- HTA

Thank you!