



Federal Institute
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Strategies for drug development in Spinal muscular atrophy (SMA) Type 1 - A regulatory perspective -

Dr. Marion Haberkamp, MD
BfArM, Bonn, Germany
SAWP (EMA)
CNSWP (EMA)

Disclaimer

- No CoI
- The content of this talk is my own and does not necessarily reflect the official views of the Federal Institute of Drugs and Medical Devices (BfArM) or the European Medicines Agency (EMA).
- All information discussed is publically available.

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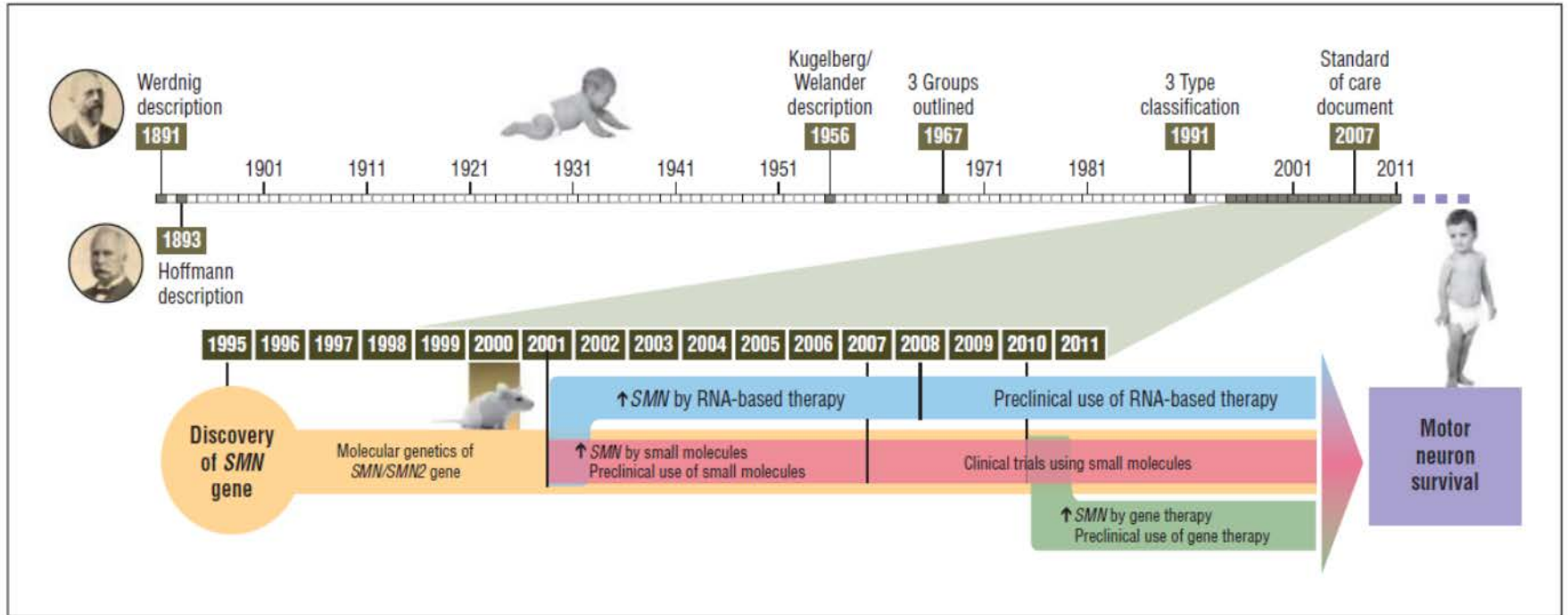
SMA type 1 - Werdnig-Hoffmann disease

- Autosomal recessive disorder with an estimated incidence of 1 in 6,000-10,000 live births
- Leading genetic cause of mortality in infants and toddlers
- 1:40- 1:60 of the general population are SMN1 mutation carriers (2%)
- Type 1 is the most severe and common type, accounts for about 50% of patients
- Onset before 6 months of age and high mortality within the first 2 years of life (68%-30%)
- Selective degeneration of alpha motor neurons in the ventral horn of the spinal cord and brainstem:
 - “floppy babies” with profound hypotonia, often no control of head movement, unable to sit without support
 - paradoxical breathing (inward bony thorax movement with outward abdominal movement during inspiration) and a bell-shaped upper torso
 - bulbar denervation results in tongue fasciculation and weakness with poor suck and swallow, nutritional deficiency
 - risk of aspiration pneumonia, respiratory insufficiency
 - joint/orthopedic deformities

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SMA timeline



Stephen J. Kolb and John T. Kissel: Arch Neurol. 2011; 68(8): 979-984

Challenges in SMA clinical drug development

- High unmet medical need to reverse, delay or halt the progressive decline in motor function and disability
- Emerging treatment options
- Regulatory standards are needed to evaluate efficacy **and** safety of a prospective treatment and to
- Establish benefit/risk in a vulnerable patient group
- Ethical considerations with respect to prolongation of suffering
- Choice between palliative care and intervention

Clinical disease classification

| | Age of onset | Highest function achieved | Natural age at death |
|---|--------------|---------------------------------|----------------------|
| Type 0 | Prenatal | Respiratory support | < 1month |
| Type I (severe, Werdnig-Hoffmann disease) | 0-6 months | Never sit | < 2 years |
| Type II (intermediate) | 7-18 months | Sit never stand | > 2 years |
| Type III (mild, Kugelberg-Welander disease) | > 18 months | Stand and Walk during adulthood | Adulthood |
| Type IV (adult) | 2-3 decade | Walk unaided | Adulthood |

**D'Amico et al 2011; Kolb & Kissel 2011*



Clinical classification

- Disease exists as a spectrum with a continuous range of severity
- Alternatively classify between early and late onset SMA (cut-off 6 months) for the purpose of clinical trials
- It is easier to show an effect in a homogeneous population
- > 6 months population will be very heterogeneous and needs to be characterised otherwise
- Extrapolation?

Diagnosis/ inclusion criteria

- Confirmed diagnosis of 5q-autosomal recessive SMA, including:
 - a. Genetic confirmation of homozygous loss of the SMN1 gene (95%)
 - b. Clinical history, signs or symptoms attributable to type 1 SMA, with **onset prior to the age of 3 months** and inability to sit independently (without support) at the time of screening
- SMN2 gene: two copies

Age of symptom onset for SMA type 1 subjects (Kolb et al. 2016)

| | < 1 month | 1–2 months | 2–3 months | 4–5 months | Not recorded | Total |
|---------------|-----------|------------|------------|------------|--------------|-------|
| SMA | 6 | 9 | 4 | 1 | 6 | 26 |
| SMA, SMN2 = 2 | 6 | 5 | 3 | 1 | 1 | 16 |

Diagnosis/2

- Narrow therapeutic time-window
- Efforts to enroll patients as soon as possible after diagnosis and ideally prior to onset of significant denervation
- Identification of early-symptomatic or even pre-symptomatic children?
- Should newborn screening (NBS) be recommended?
- Seen controversial
- After approval of effective treatments?

Symptomatic therapy of SMA

Special Issue Article

Consensus Statement for Standard of Care in Spinal Muscular Atrophy

Ching H. Wang, MD, PhD, Richard S. Finkel, MD, Enrico S. Bertini, MD, Mary Schroth, MD, Anita Simonds, MD, Brenda Wong, MD, Annie Aloysius, MRCSLT, HPC, Leslie Morrison, MD, Marion Main, MCSP, MA, Thomas O. Crawford, MD, Anthony Trela, BS, and Participants of the International Conference on SMA Standard of Care

Journal of Child Neurology
Volume 22 Number 8
August 2007 1027-1049
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10.1177/0883073807305788
<http://jcn.sagepub.com>
hosted at
<http://online.sagepub.com>

Implementation of “the consensus statement for the standard of care in spinal muscular atrophy” when applied to infants with severe type 1 SMA in the UK

H Roper,¹ R Quinlivan² on Behalf of Workshop Participants



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Arch Dis Child 2010;**95**:845–849. doi:10.1136/adc.2009.166512



Symptomatic therapy of SMA

J Neurol (2014) 261:152–163
DOI 10.1007/s00415-013-7154-1

ORIGINAL COMMUNICATION

Mapping the differences in care for 5,000 Spinal Muscular Atrophy patients, a survey of 24 national registries in North America, Australasia and Europe

Catherine L. Bladen · Rachel Thompson · Jacqueline M. Jackson · Connie Garland · Claire Wegel · Anna Ambrosini · Paolo Pisano · Maggie C. Walter · Olivia Schreiber · Anna Lusakowska · Maria Jedrzejowska · Anna Kostera-Pruszczyk · Ludo van der Pol · Renske I. Wadman · Ole Gredal · Ayse Karaduman · Haluk Topaloglu · Ozgur Yilmaz · Vitaliy Matyushenko · Vedrana Milic Rasic · Ana Kosac · Veronika Karcagi · Marta Garami · Agnes Herczegfalvi · Soledad Monges · Angelica Moresco · Lilien Chertkoff · Teodora Chamova · Velina Guerguelcheva · Niculina Butoianu · Dana Craiu · Lawrence Korngut · Craig Campbell · Jana Haberlova · Jana Strenkova · Moises Alejandro · Alatorre Jimenez · Genaro Gabriel Ortiz · Gracia Viviana Gonzalez Enriquez · Miriam Rodrigues · Richard Roxburgh · Hugh Dawkins · Leanne Youngs · Jaana Lahdetie · Natalija Angelkova · Pascal Saugier-veber · Jean-Marie Cuisset · Clemens Bloetzer · Pierre-Yves Jeannet · Andrea Klein · Andres Nascimento · Eduardo Tizzano · David Salgado · Eugenio Mercuri · Thomas Sejersen · Jan Kirschner · Karen Rafferty · Volker Straub · Kate Bushby · Jan Verschuuren · Christophe Beroud · Hanns Lochmüller



Primary Endpoint

- Survival and other end-of-life measures (e.g. time to full-time ventilation) are important outcomes, however, highly variable due to variable standard of care
- Gross motor function milestones (proportion of infants sitting after 12 months) as primary endpoint preferred (De Sanctis et al. 2016)
- Should be standardized: e.g. sitting without support for 5 seconds
 - video-recorded in a standardized manner
 - centrally reviewed
 - independent raters

De Sanctis R. et al. Developmental milestones in type I spinal muscular atrophy; Neuromuscular disorders 26 (2016) 754-759

Secondary Endpoints

- Survival/end-of-life measures as key secondary endpoint
- Motor performance scales
- Respiratory function (e.g. inductive plethysmography)
- Improvement in asynchrony between diaphragmatic (abdominal) breathing and thoracic cage-driven breathing
- QoL /PedsQL
- Caregiver burden
- Growth parameters
- Electrophysiological measures (CMAP, MUNE, EIM)

Motor performance scales in SMA type 1

- **CHOP-INTEND** (Children's Hospital of Philadelphia Test of Neuromuscular Disorders)
- **TIMPSI** (Test of Infant Motor Performance Screening Items)
- **GMFM** (Gross Motor Function Measure)
- **HFSME** (Hammersmith Functional Motot Scale Expanded)
- **MFM** (Motor Function Measure)
- **EK2** (Egen Classification Scale v2)

Cano SJ et al: Rasch analysis of clinical outcome measures in spinal muscular atrophy; Muscle Nerve 2014; 49(3):422-430

Trial design

- Placebo controlled studies are the optimal design
- Open-label designs versus historical controls acceptable in SMA type 1
- Rapid decline and low life expectancy
- Never achieve motor milestone sitting (De Sanctis et al. 2016)
- Primary endpoint chosen should not be subject to bias
- Known natural history, no need for internal control arm
- Data in the immediate postnatal period are scarce
- Ideally patients should be carefully matched

De Sanctis R. et al. Developmental milestones in type I spinal muscular atrophy; Neuromuscular disorders 26 (2016) 754-759

Study duration

- Depends on the mechanism of action and endpoint chosen
- Modification or slowing disease progression
- 12 months data are required
- Maintenance of effect needs to be assessed: long-term treatment
- Open label extension study

How many trials

- Orphan disease scenario
- One well-conducted study could be sufficient for type 1 SMA
- Data should be sufficient to allow benefit/risk assessment
- Second study across the disease spectrum (type2/3) will be needed:
 - » Differences in physiology
 - » Evolving metabolic pathways
 - » Differing profile of comorbidities

Role of biomarkers

- Enrichment, outcome
- Electrophysiological (CMAP, EIM), protein and molecular biomarkers (SMN mRNA levels, SMN protein levels) , muscle mass quantification may be used to better characterize the population (Kolb et al. NeuroNEXT biomarker study, Annals for Clinical and Translational Neurology, 2016)
- SMA transcripts and proteins can be used to indicate pharmacological activity of a drug
- Electrophysiologic markers could be used as a biomarker of change in neuromuscular function
- **No surrogacy established yet**
- Need to identify and validate physiological and molecular biomarkers

What will be offered

- Early involvement of SAWP for **Scientific advice and Protocol assistance**
- **CHMP Qualification Opinion** on the acceptability of a specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data.
- **CHMP Qualification Advice on future protocols and methods for further method development towards qualification**, based on the evaluation of the scientific rationale and on preliminary data submitted.

Early access tools: Overview

- 1. Conditional MA:** Unmet medical need, seriously debilitating or life-threatening disease. **Early approval on the basis of less complete data.** Emphasis on importance of prospective planning and early dialogue.
- 2. ACCELERATED ASSESSMENT:** Major public health interest, unmet medical need. **Reduce assessment time from 210 to 150 days.** Optimisation of the assessment timetable. Emphasis on the importance of early dialogue
- 3. PRiority MEdicines (PRIME):** New scheme for unmet medical needs and major public health interest. Early interaction at proof of principle or proof of concept.

<http://www.ema.europa.eu>

Issues for discussion

- Definition of populations:
Early diagnosis versus pre-symptomatic patients; NBS
- Importance/improvement of patient registries
- Validation and identification of Biomarkers
- Extrapolation
- Maintenance of effect
- Studies in case of approval of one drug

Thank you very much for your attention!

Contact

Federal Institute for Drugs and Medical Devices
Division 34, Neurology, Psychiatry and Ophthalmology
Kurt-Georg-Kiesinger-Allee 3
D-53175 Bonn

Contact person
Dr. med. Marion Haberkamp
marion.haberkamp@bfarm.de
www.bfarm.de
Tel. +49 (0)228 99 307-3365