Spinal Muscular Atrophy – Treatment Network

Monday 28th November 2022

Event will commence at 13:30

Information

- *All organisers and speakers and declare no conflict of interest*

- *This meeting has been supported by Novartis Gene Therapies via provision of funding to cover use of a virtual event platform and logistical support. Novartis Gene Therapies had no involvement in the agenda or speaker selection.*

Agenda

Part A - The importance of early diagnosis

Primary audience: All involved in SMA care, with a focus on health visitors, general and community paediatricians, GP trainees, neonatologists.

Co-chairs: Drs Imelda Hughes and Gary McCullagh, Consultant Paediatric Neurologists, Royal Manchester Children's Hospital

Start	Duration	Topic	Learning objective	Speaker
1:30	5 mins	**Welcome**		Co-Chairs
1:35	20 mins	**Case studies of new presentations**	Here we will explore 2 different cases of children who ultimately received a diagnosis of SMA, how the diagnostic journey evolved, the experience of the healthcare professionals, and the outcomes for each child	Dr Diarmuid Kerrin, Barnsley Hospital NHS Foundation Trust Dr Gary McCullagh, Royal Manchester Children's Hospital
1:55	25 mins	**What to look for**	Here we take a look at what best practice tells us about how to identify suspect SMA, with the aim of arming professionals involved in the care of young children with the right skills to make timely referral. We'll also share the experience of a particular family and their journey.	Rajesh Madhu, Alder Hey Children's Hospital
2:20	30 mins	**New born screening**	Here we hear discuss the effectiveness of new-born screening on pre-symptomatic patients, pilots underway and the approaches different countries have taken.	Dr Sithara Ramdas, Oxford University Hospitals NHS Foundation Trust
2:50	10 mins	**Questions & discussion**		
3:00	10 mins	**Comfort break**		

Agenda

Part B - Treatment and management

Primary audience: All involved in SMA care, likely of special interest to those involved in the later elements of the pathway such as consultant neurologists/paediatricians, specialist nurses, Allied Health Professionals.

Co-chairs: Drs Imelda Hughes and Gary McCullagh, Consultant Paediatric Neurologists, Royal Manchester Children's Hospital

Start	Duration	Topic	Learning objective	Speaker
3:10	25 mins	**Respiratory care**	Here we will explore the importance of respiratory assessment and management, develop comprehensive awareness of respiratory management including prevention, secretion clearance, ventilatory support, management of acute exacerbations	Dr Stuart Wilkinson, Royal Manchester Children's Hospital
3:35	25 mins	**Physiotherapy and dietetics care**	Here we'll explore the topics of secretion management and augmented cough in the SMA patient	Sinead Warner, Royal Manchester Children's Hospital
4:00	30 mins	**The evolving phenotype of the SMA population**	First we'll have a short talk on the recent development of treatments is extending the lives of children with SMA, and how this changes the phenotypic landscape. We'll then have an open discussion with attendees on the implications for care.	Anne-Marie Childs, Leeds Teaching Hospitals NHS Trust
4:30	15 mins	**Questions & discussion**		

Housekeeping

- We ask for attendees to remain muted for the duration of the meeting to ensure good sound quality and clarity of the speakers
- The Chair may ask you to unmute if you have a question
- Questions are very welcome – please use the chat function and these will be responded to at the end of each topic

Newborn screening for Spinal muscular atrophy

Dr Sithara Ramdas

Consultant Paediatric Neurologist, John Radcliffe Hospital, Oxford

Honorary Senior Clinical Lecturer, MDUK Neuromuscular Centre, Department of Paediatrics, University of Oxford

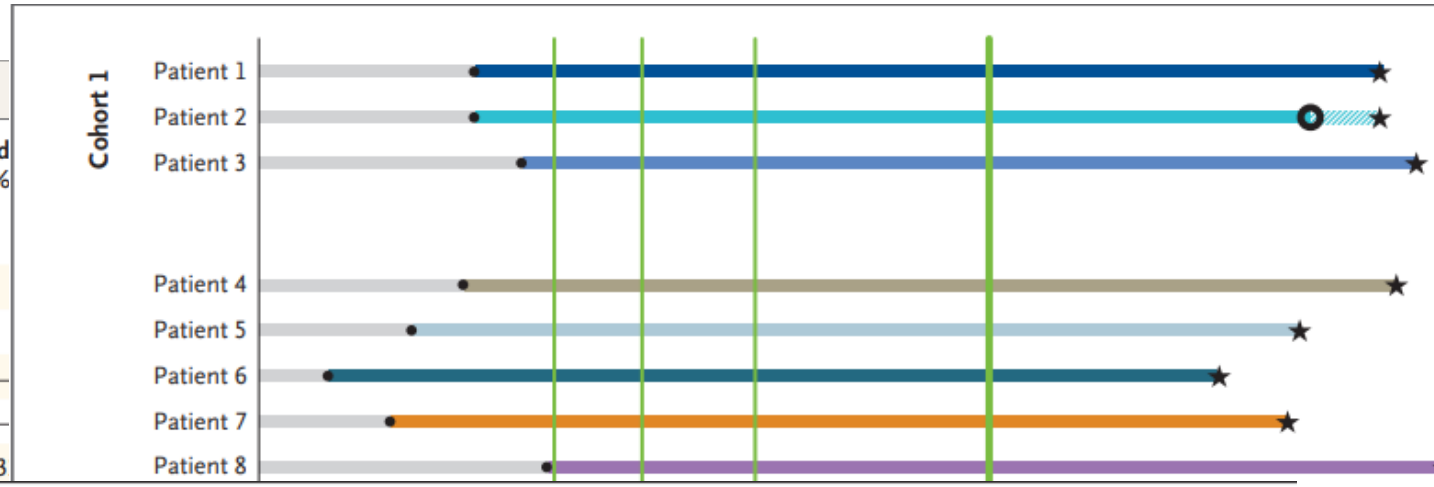
Disclosures

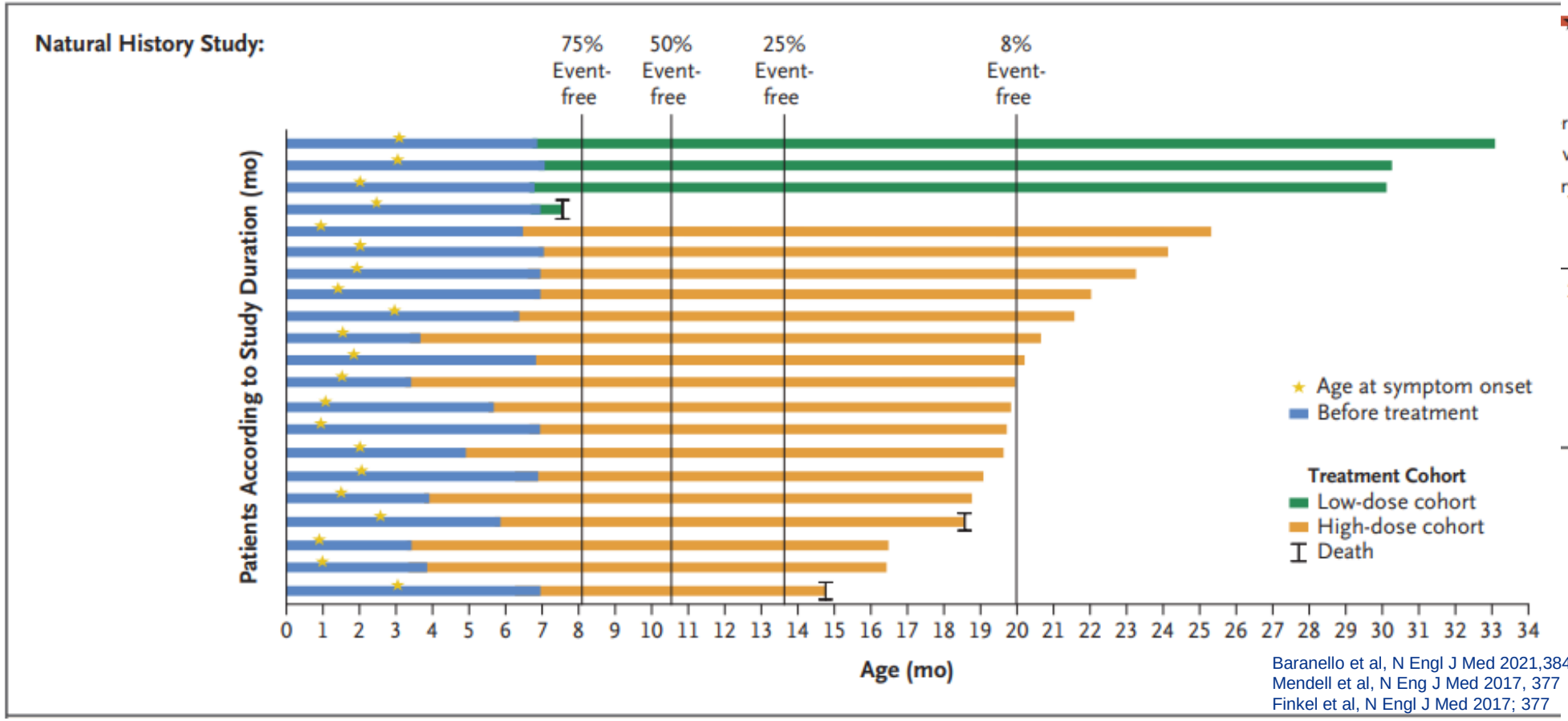
- Served on advisory board for Novartis, Sarepta, Argenx and Roche
- Investigator in clinical trials for Sarepta, Roche, Wave, Genetx, Argenx, and Santhera
- Speaker fees for educational meetings from Novartis

NICE approved treatments

Table 2. Primary and Secondary End Points.*

End Point	Nusinersen Group	Control Group	Hazard (95%
	no./total no. (%)		
Primary end points			
Motor-milestone response†			
Interim analysis	21/51 (41)	0/27	—
Final analysis	37/73 (51)	0/37	—
death or use of permanent assisted ventilation‡	49/80 (61)	13/41 (32)	0.53 (0.3
Secondary end points§			
CHOP INTEND response¶			
No death			
No use of permanent assisted venti			
CMAP response‖			
No death or use of permanent assis among those with disease du at screening‡			
No death or use of permanent assis among those with disease du at screening‡			





rapy infusion
visit
ry event

29 30 31 32

Baranello et al, N Engl J Med 2021,384
Mendell et al, N Eng J Med 2017, 377
Finkel et al, N Engl J Med 2017; 377

Do we need newborn screening in SMA

HOW CAN WE
MAKE IT
BETTER

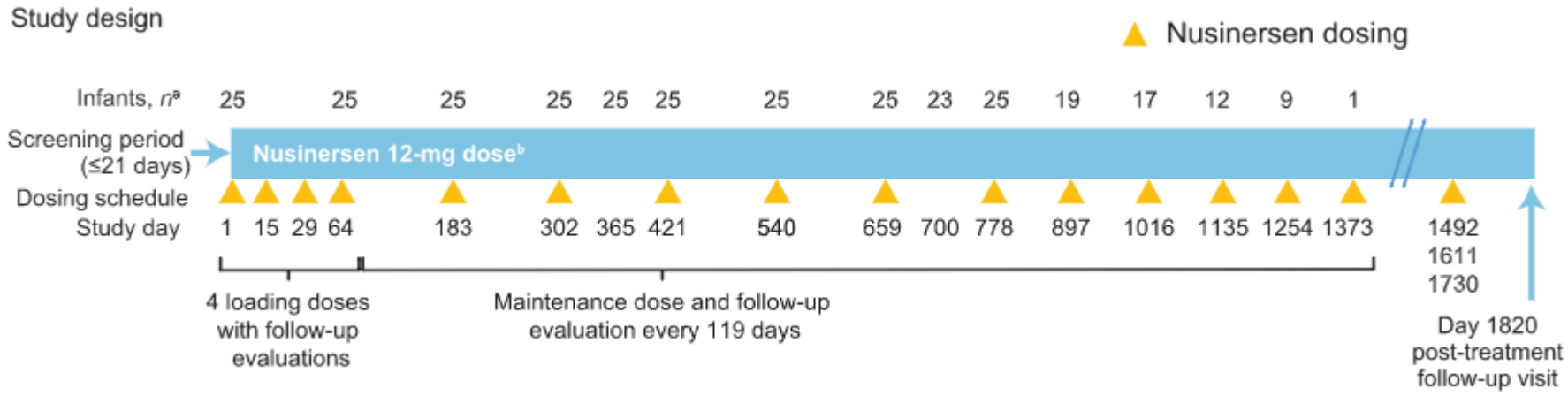
NURTURE

- Phase 2,open-label, single-arm, multinational study to evaluate the long-term safety and efficacy of intrathecal nusinersen in infants who initiate treatment age ≤6 weeks at first dose, clinically presymptomatic, and genetically diagnosed with SMA with 2 or 3 *SMN2* copies.

Primary endpoint: Time to death or respiratory intervention (≥6 hours/day continuously for ≥7 days or tracheostomy

Secondary endpoints:
- Survival
- Motor milestones : WHO criteria, HINE-2, CHOP
- Growth
- Feeding and nutrition

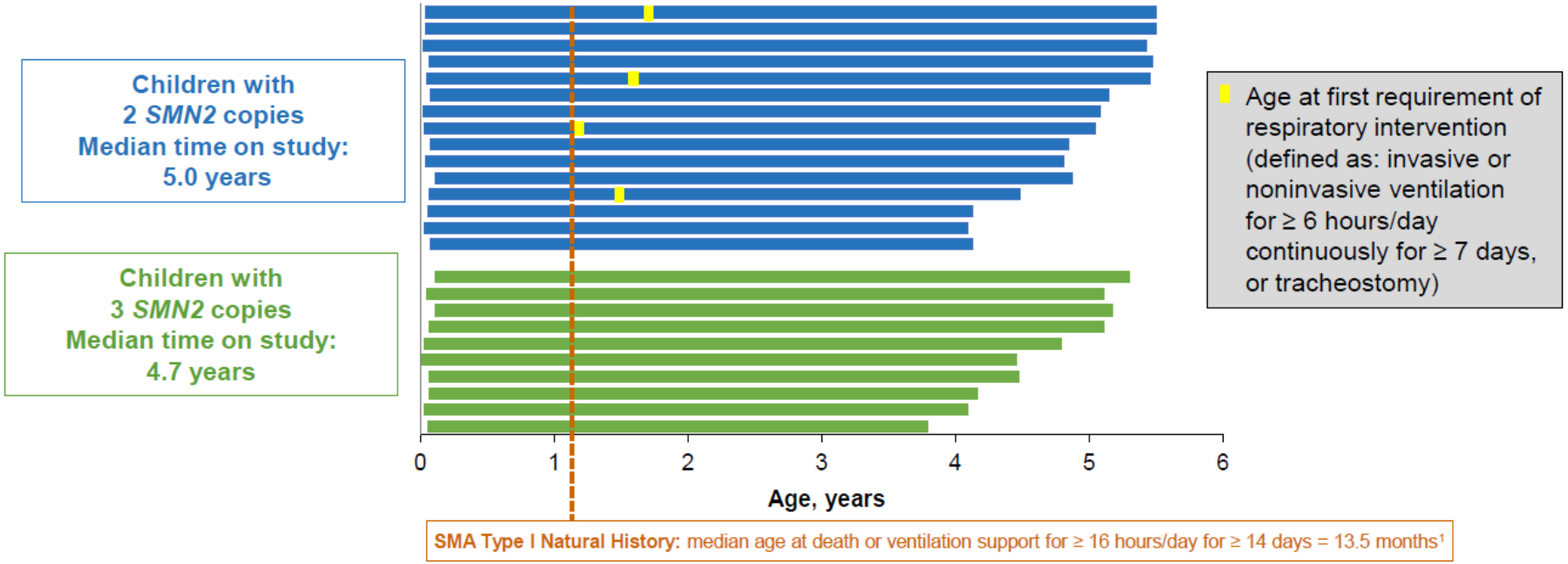
De Vivo et al. Neuromuscular Dis 2019



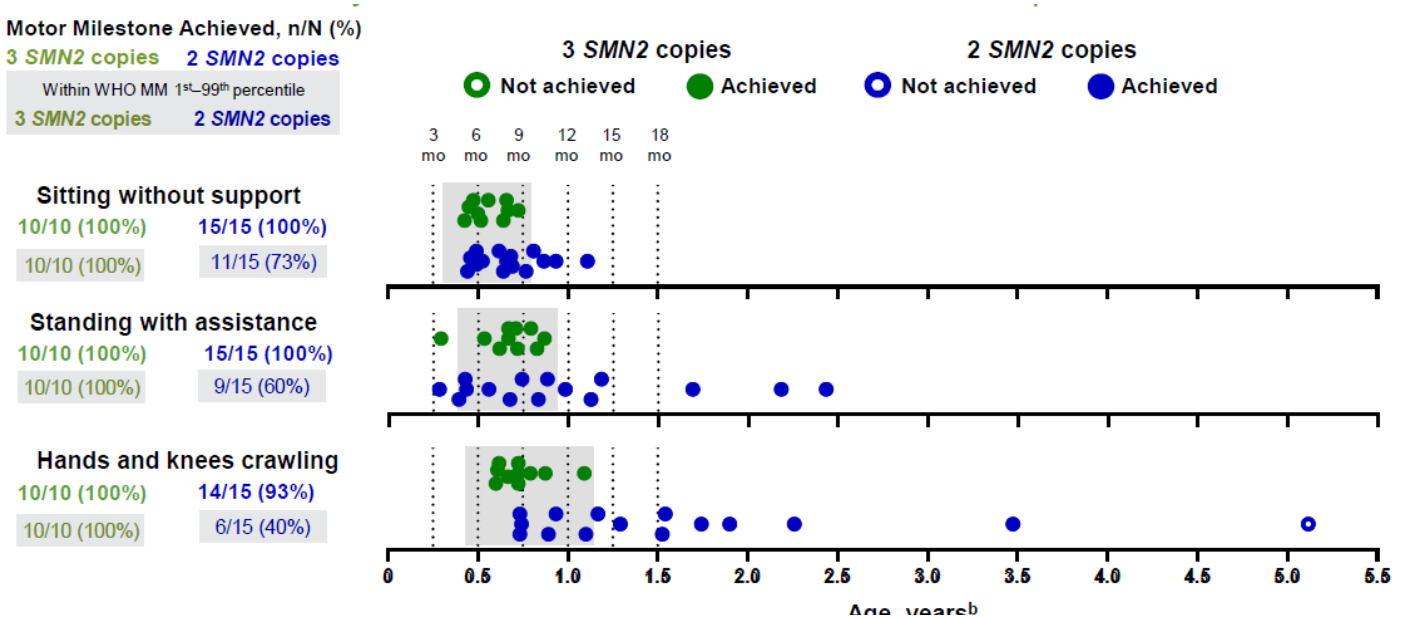
- 25 infants
- 15 with two SMN2 copies, 10 with three SMN2 copies)
- Median age at first dose 22.0 (3–42) days
- Median age at last visit was 3.8 (range, 2.8–4.8) y
- Median duration in study 3.8 (range, 2.8–4.7) y

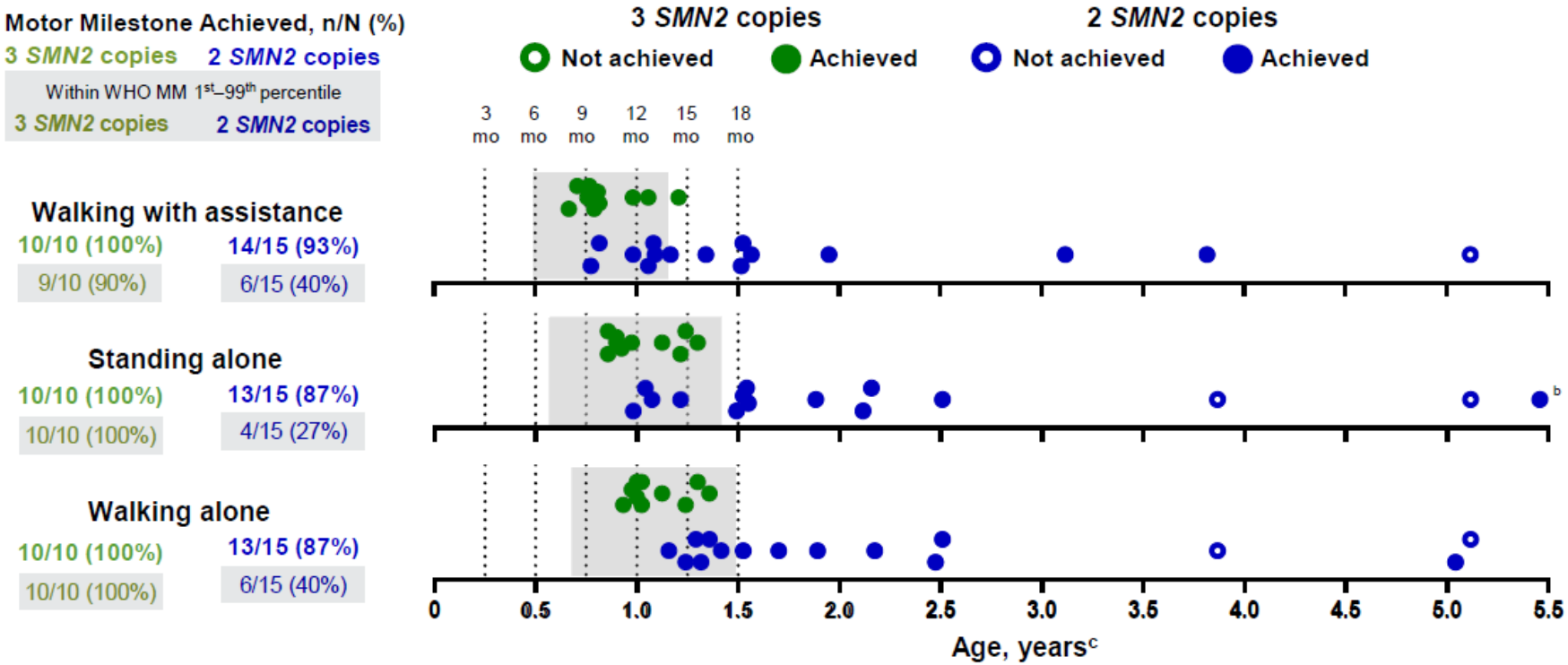
De Vivo et al Neuromusc Dis 2019
Swoboda et al ICMD pres 2021

All children were alive and none required permanent ventilation[a] or tracheostomy

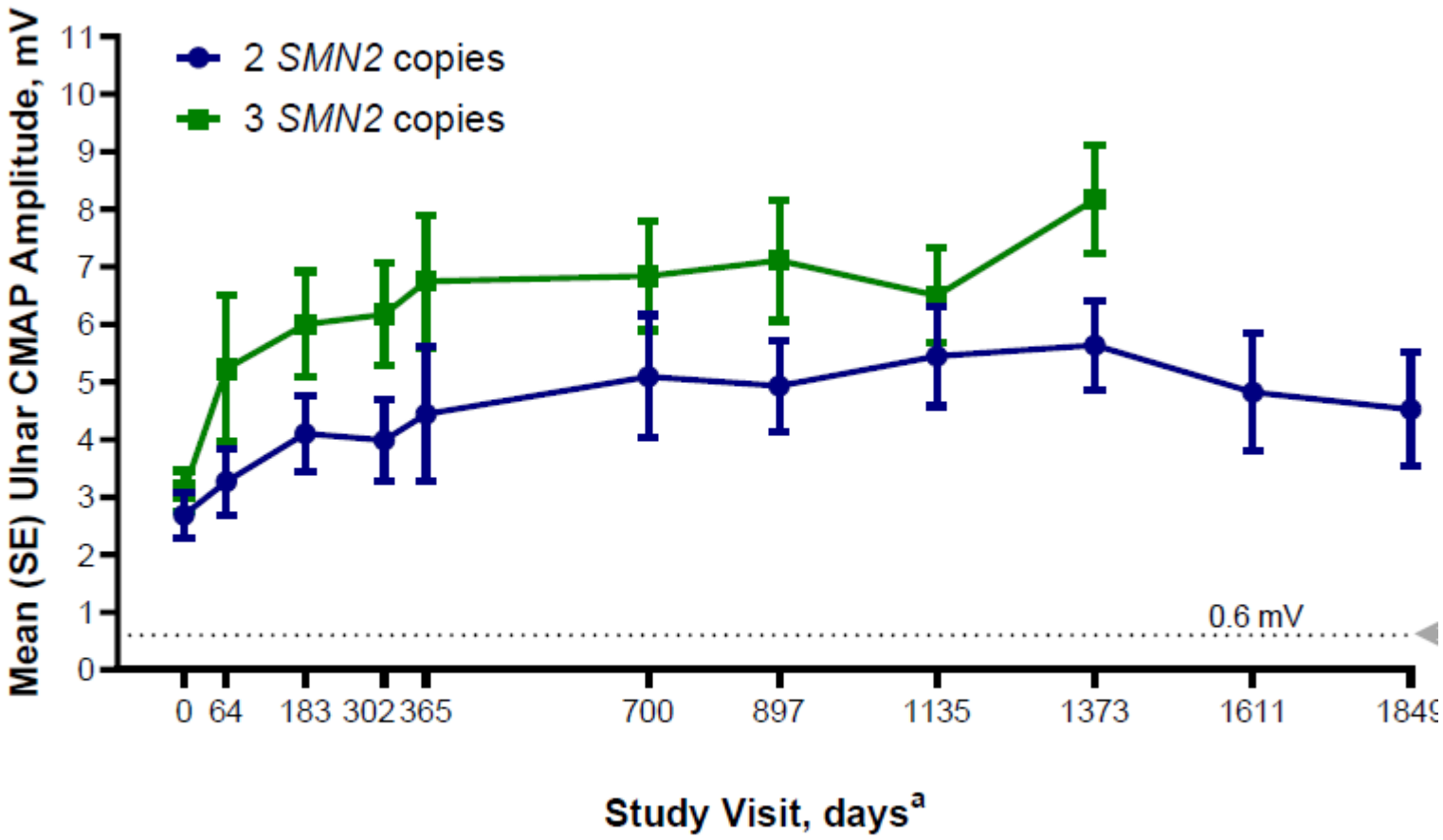


Kuntz N et al CSMA 2022





Kuntz N et al CSMA 2022



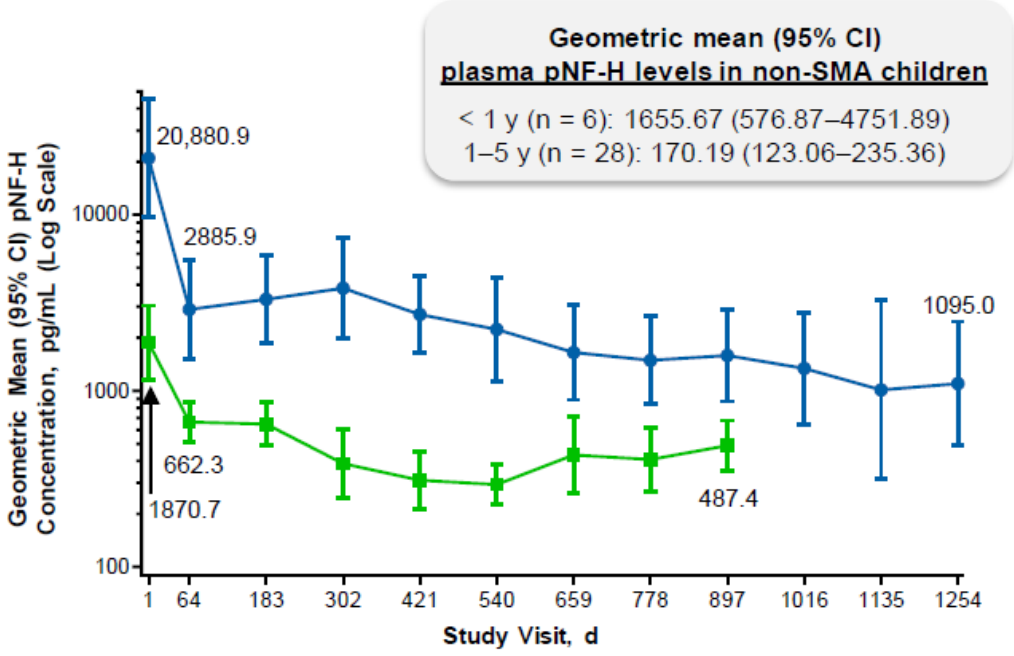
3 *SMN2* copies	10	9	10	10	10	9	10	8	10		
2 *SMN2* copies	14	14	14	14	15	14	13	15	12	7	5

Range of normal values in healthy infants[1]

Age	Ulnar nerve CMAP amplitude, mV
Neonate	1.6–7.0
1–6 mo	2.5–7.4
7–12 mo	3.2–10.0

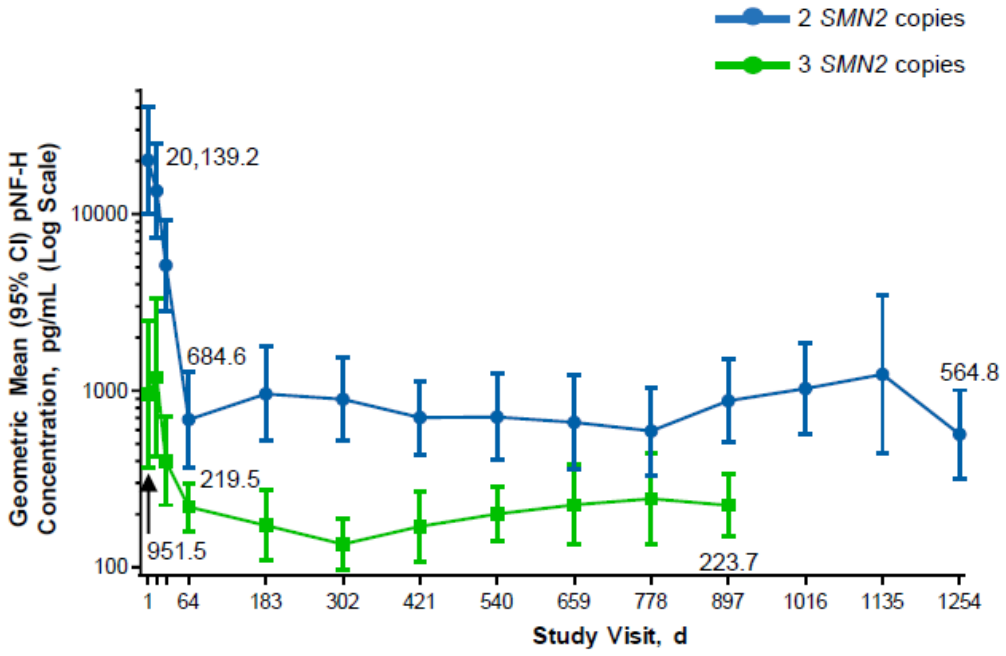
Plasma and CSF pNF-H Levels Rapidly Declined During the Loading Period and Then Stabilized

Plasma



2 *SMN2* copies, n	13	14	14	13	14	13	14	14	12	11	6	5
3 *SMN2* copies, n	9	9	10	10	10	9	10	9	6			

CSF



2 *SMN2* copies, n	14	13	13	14	14	14	13	13	11	11	7	6
3 *SMN2* copies, n	9	10	10	9	10	10	10	9	6			

Swoboda et al ICMD 2021

SPR1NT

A Phase 3, open-label, single-arm, multi-centre trial designed to evaluate the safety and efficacy of a single-dose IV infusion of ZOLGENSMA in presymptomatic patients with a genetic diagnosis of SMA and 2 or 3 copies of *SMN2* who were ≤6 weeks of age at the time of treatment[1,2]

2 copy cohort

- 14 infants
- Primary endpoint: Independent sitting for ≥30 seconds at any visit upto 18months
- Secondary endpoints: Survival, ventilatory requirements and weight gain without feeding support

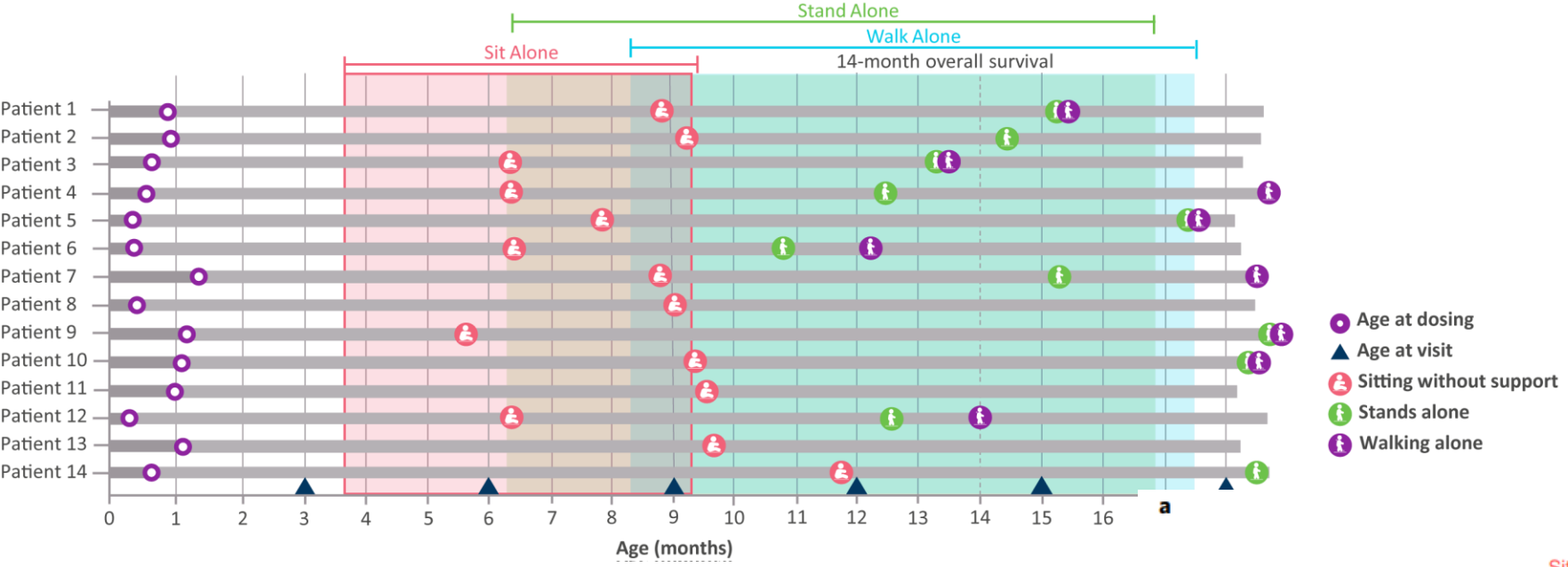
3 copy cohort

- 15 infants
- Primary endpoint: Independent standing for ≥3 seconds at any visit upto 24months
- Secondary endpoints: Independent walking for ≥ 5 seconds at any visit upto 24 months

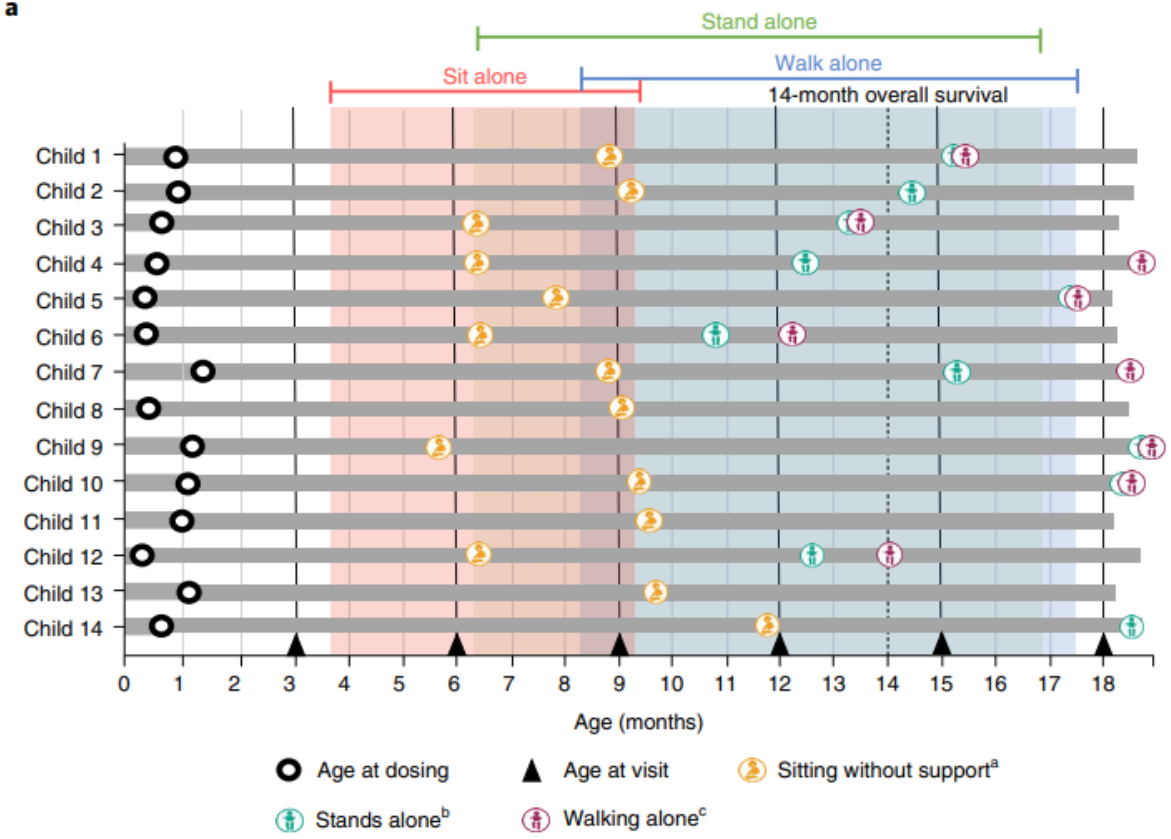
Baseline characteristics

Patient characteristics	2 copies of *SMN2* (N=14)
Mean (SD) age at dosing, days*	20.6 (7.9)
Mean (SD) gestational age at birth, weeks	38.2 (1.4)
Mean (SD) age at diagnosis, days†	7.2 (4.8)
Mean (SD) weight at baseline, kg	3.6 (0.39)
Sex, n (%)	
Male	4 (29)
Female	10 (71)
Modality of diagnosis, n (%)	
Prenatal testing	5 (36)
Newborn screening	9 (64)

Patient characteristics	3 copies of *SMN2* (N=15)
Mean (SD) age at dosing, days*	28.7 (11.68)
Mean (SD) gestational age at birth, weeks	38.8 (1.47)
Mean (SD) age at diagnosis, days†	9.9 (7.69)
Mean (SD) weight at baseline, kg	4.1 (0.53)
Sex, n (%)	
Male	6 (40)
Female	9 (60)
Modality of diagnosis, n (%)	
Prenatal testing	1 (7)
Newborn screening	13 (87)
Other	1 (7)



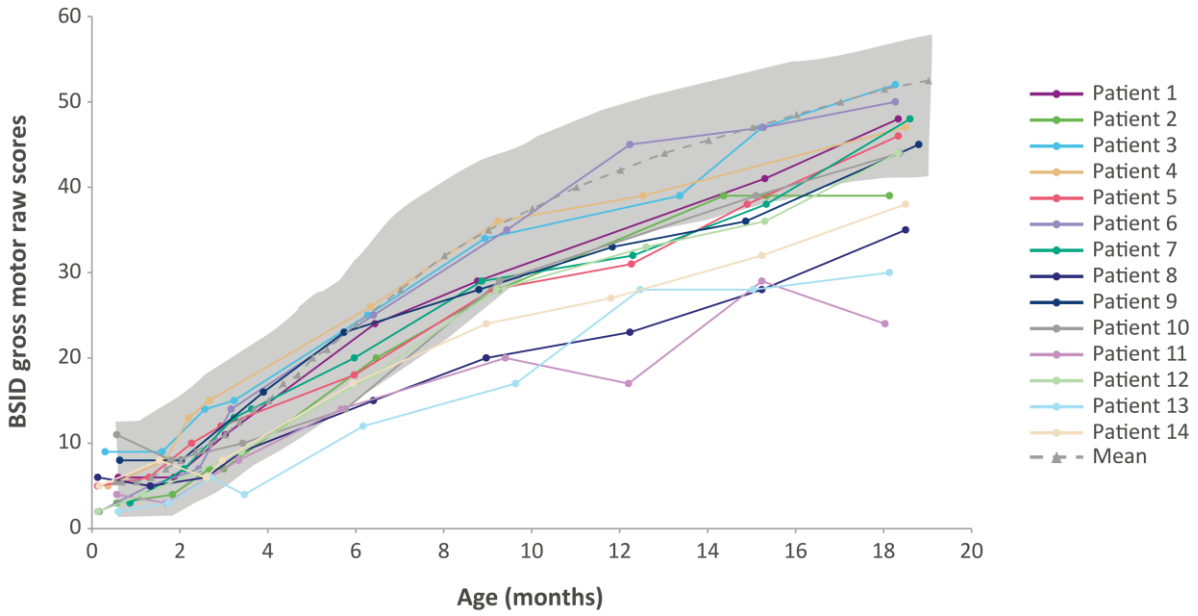
11/14 – independent standing
9/14 independent walking



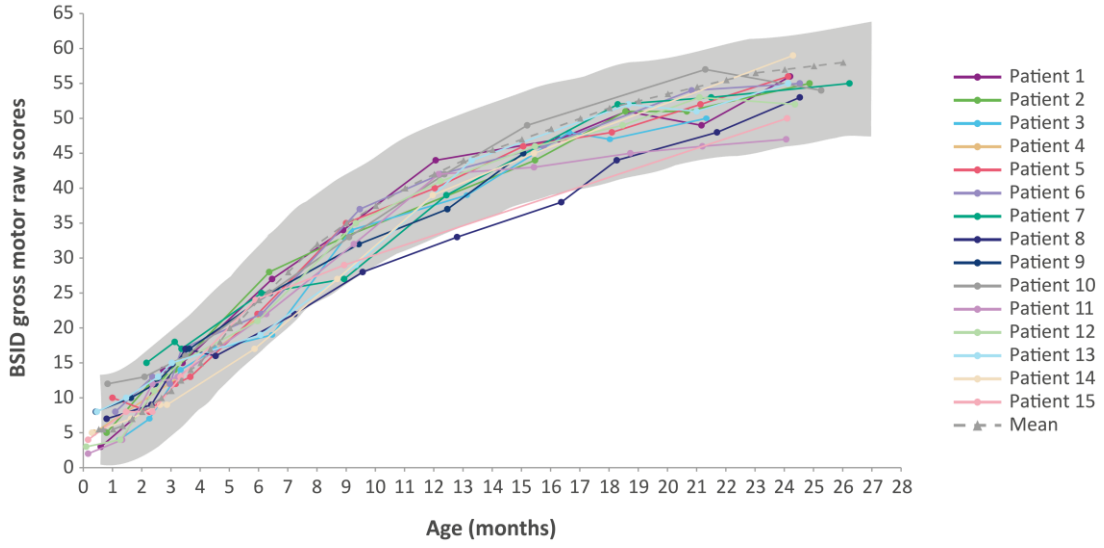
14/15 – 93% walking
73% within normal WHO window

Strauss K et al 2022 Nat Med

Bayley-III Scales of Infant and Toddler Development- Gross motor

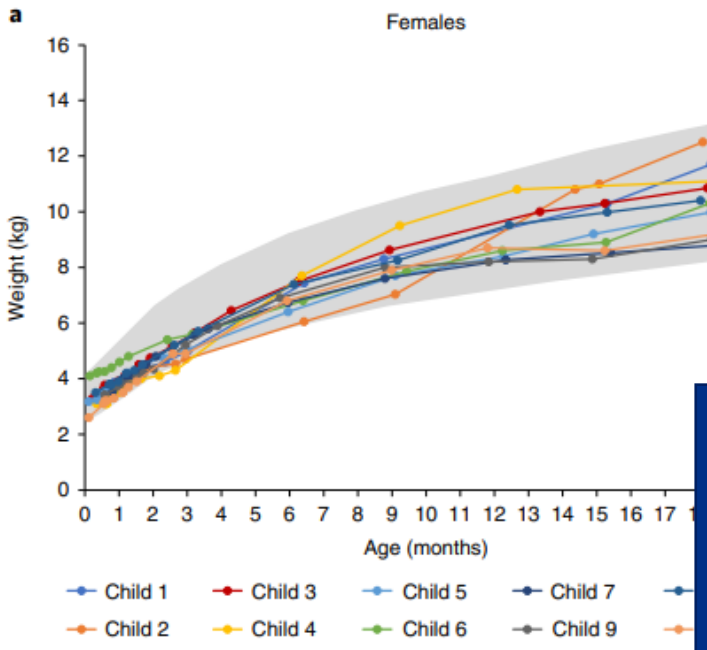


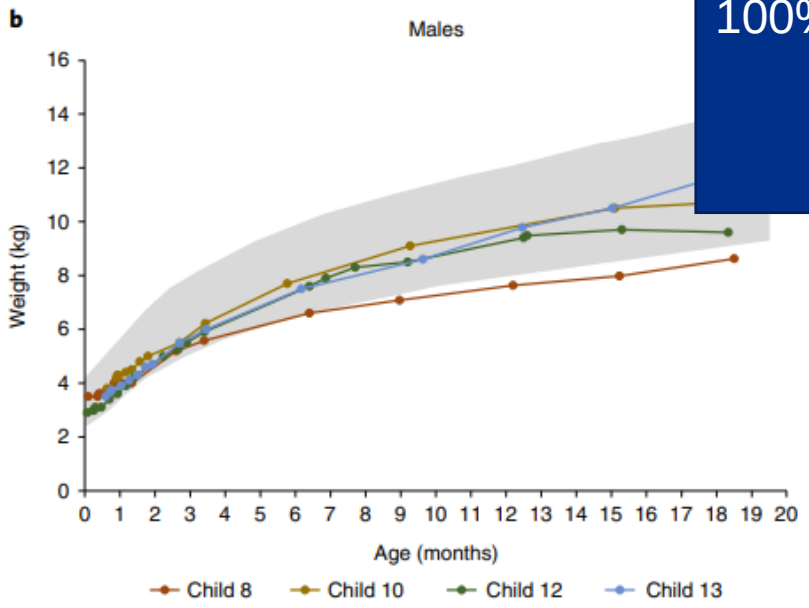
2 copies of SMN 2

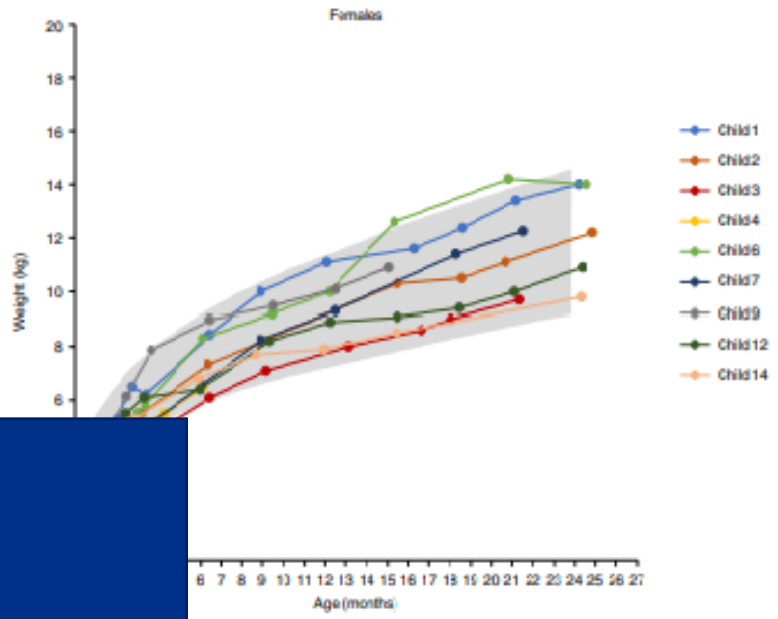


3 copies of SMN 2

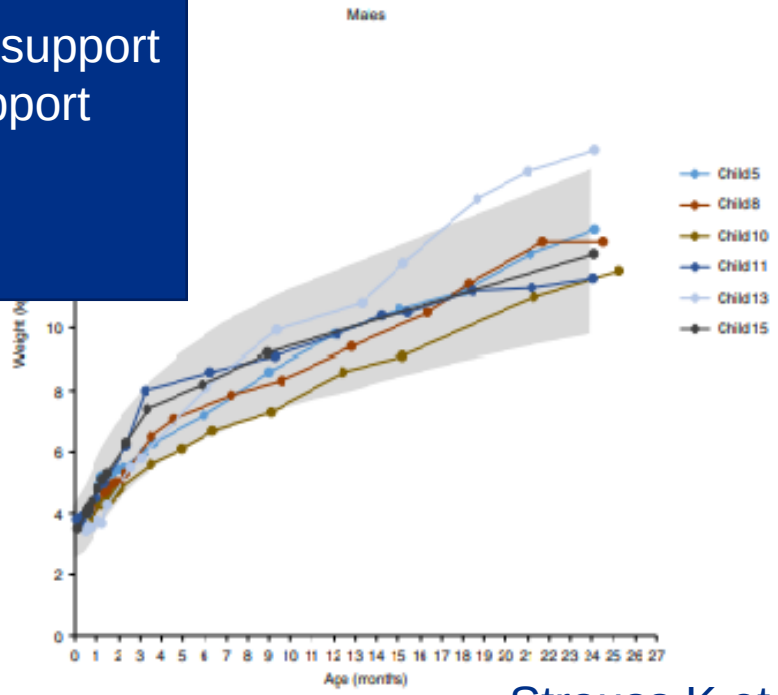
Strauss K et al Nat Med 2022







100% survival
100% off any respiratory support
100% off any feeding support



Strauss K et al 2022 Nat Med

RAINBOW FISH

- Open-label, single-arm, multinational study to evaluate the efficacy, safety, pharmacokinetics/pharmacodynamics of risdiplam in infants who initiate treatment age ≤6 weeks at first dose, clinically presymptomatic, and genetically diagnosed with SMA regardless of SMN2 copy number

Primary endpoint: Proportion of infants who are sitting without support for ≥5 seconds at Month 12

Secondary endpoints:

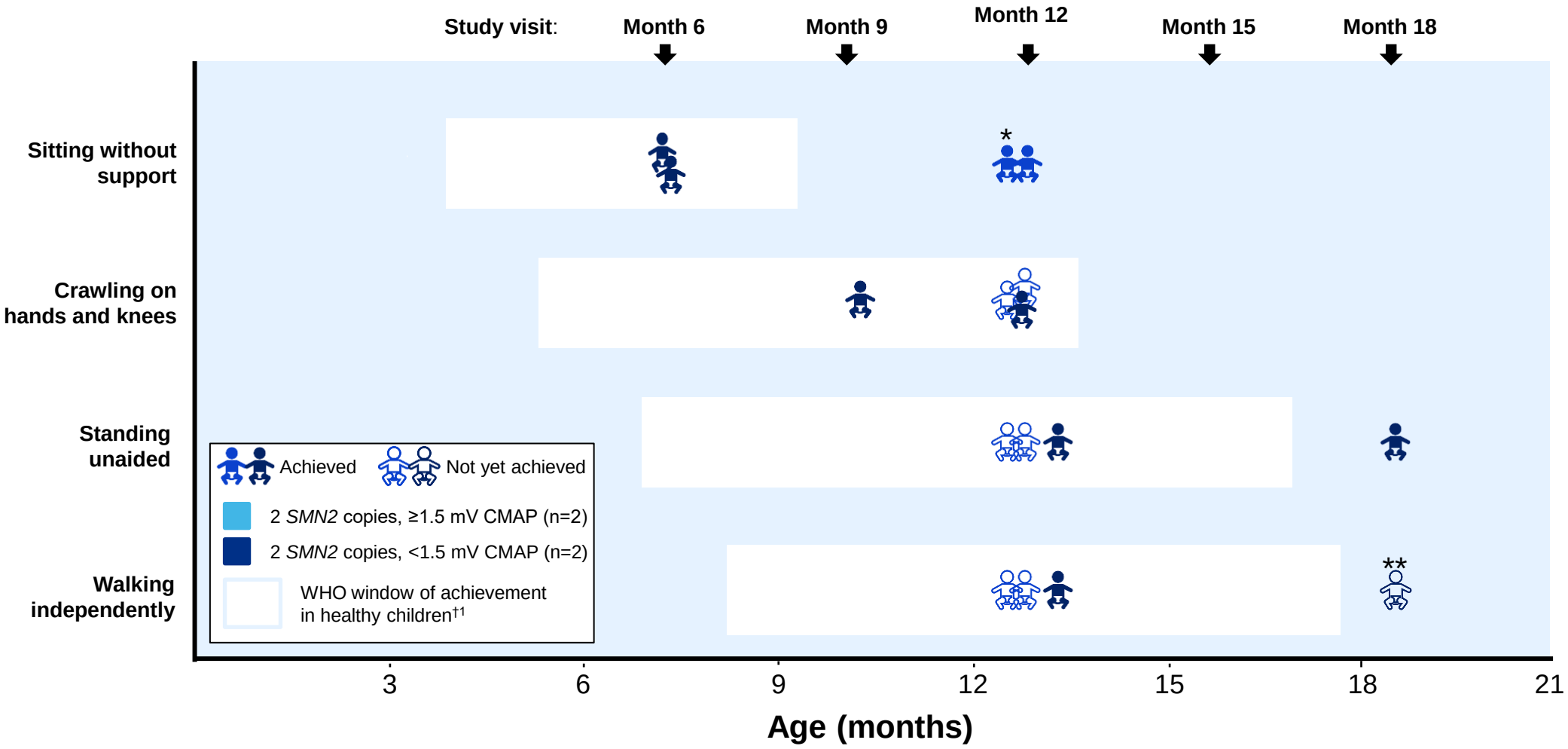
- Development of clinically manifested SMA
- Survival and permanent ventilation
- Achievement of motor milestones as defined by the HINE-2 and BSID-III Gross Motor Scale
- CHOP-INTEND total score
- Growth measures
- Ability to swallow and feed orally
- CMAP amplitude
- PK/PD **and** Safety

De Vivo et al. Neuromuscular Dis 2019

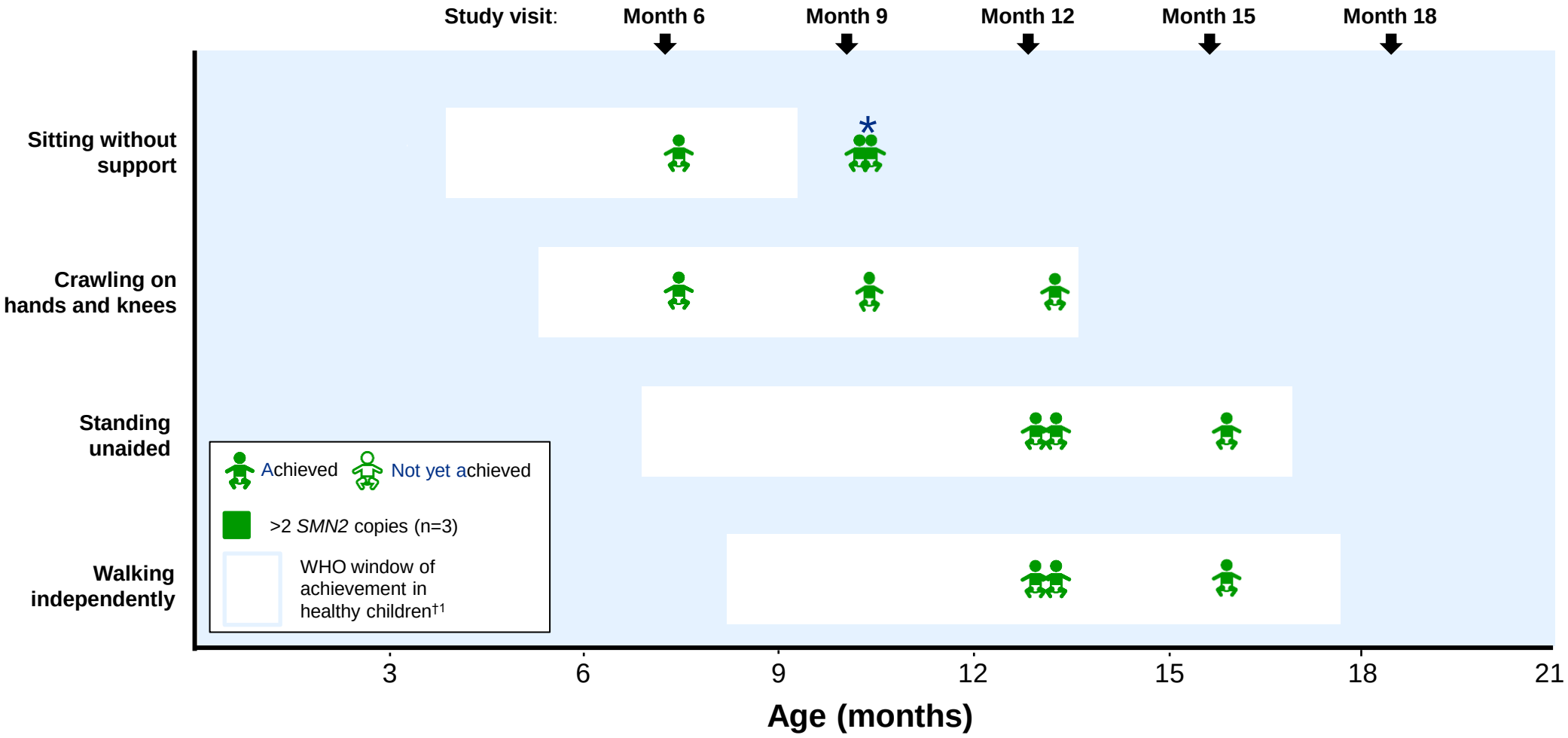
- 12 infants enrolled
- Median age at first dose was 28.5 days (range: 16–40 days)

- 7 infants treated for > 12 months
  - 100% alive and without any respiratory support
  - 100% orally fed
  - 100% improving motor milestones

SMN 2 copies


Study visit:
Month 6
Month 9
Month 12
Month 15
Month 18
Sitting without support
Crawling on hands and knees
Standing unaided
Walking independently
*
**
Achieved
Not yet achieved
2 SMN2 copies, ≥1.5 mV CMAP (n=2)
2 SMN2 copies, <1.5 mV CMAP (n=2)
WHO window of achievement in healthy children†1
3
6
9
12
15
18
21
Age (months)

>2 copies of SMN 2



3 clinical trials in pre-symptomatic SMA

- Early treatment has substantial benefit across domains with motor development in many cases with normal WHO window for motor milestones

Next
Steps?

RESEARCH Open Access

Newborn screening for spinal muscular atrophy in Germany: clinical results after 2 years

Katharina Vill[1†], Oliver Schwartz[2†], Astrid Blaschek[1], Dieter Gläser[3], Uta Nennstiel[4], Brunhilde Wirth[5], Siegfried Burggraf[6], Wulf Röschinger[6], Marc Becker[6], Ludwig Czibere[6], Jürgen Durner[6,7], Katja Eggermann[8], Bernhard Olgemöller[9], Erik Harms[10], Ulrike Schara[11], Heike Kölbel[11†] and Wolfgang Müller-Felber[1*†]

Three years pilot of spinal muscular atrophy newborn screening turned into official program in Southern Belgium

François Boemer[1], Jean-Hubert Caberg[2], Pablo Beckers[1], Vinciane Dideberg[2], Samantha di Fiore[1], Vincent Bours[3], Sandrine Marie[4], Joseph Dewulf[4], Lionel Marcelis[5], Nicolas Deconinck[6], Aurore Daron[7], Laura Blasco-Perez[8], Eduardo Tizzano[8], Mickaël Hiligsmann[9], Jacques Lombet[10], Tatiana Pereira[10], Lucia Lopez-Granados[10], Sarvnaz Shalchian-Tehran[11], Véronique van Assche[12], Arabelle Willems[12], Sofie Huybrechts[13], Bénédicte Mast[14], Rudolf van Olden[15], Tamara Dangouloff[7] & Laurent Servais[7,16]

CMAP changes upon symptom onset and during treatment in spinal muscular atrophy patients: lessons learned from newborn screening

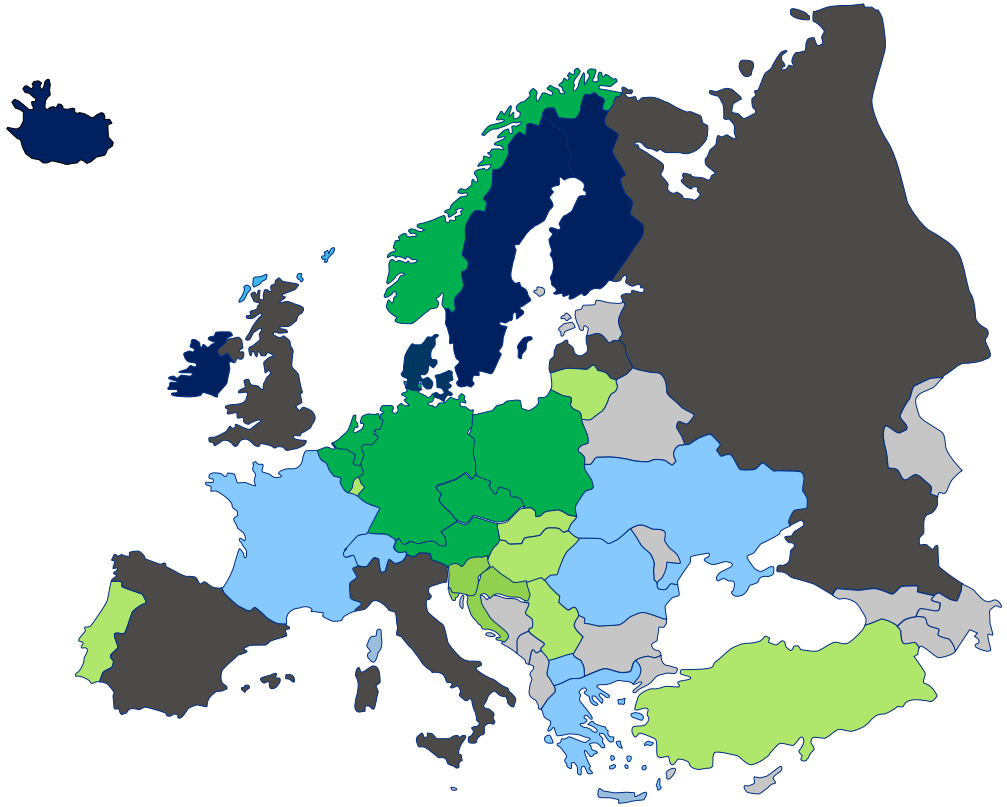
Wen-Chin Weng, MD, PhD[1,2], Yu-Kan Hsu, MD[1], Fu-Man Chang, MD[3], Chun-Yen Lin, MD, MS[4], Wuh-Liang Hwu, MD, PhD[1,2,5], Wang-Tso Lee, MD, PhD[1,2], Ni-Chung Lee, MD, PhD[1,2,5] and Yin-Hsiu Chien, MD, PhD[1,2,5]

Pilot study of population-based newborn screening for spinal muscular atrophy in New York state

Jennifer N. Kraszewski, MPH[1,2], Denise M. Kay, PhD[3], Colleen F. Stevens, PhD[3], Carrie Koval, MS[1], Bianca Haser, BS[1], Veronica Ortiz, MHS[1], Anthony Albertorio, BA[1], Lilian L. Cohen, MD, MPH[4], Ritu Jain, PhD[3], Sarah P. Andrew, BA[5], Sally Dunaway Young, PT, DPT[5], Nicole M. LaMarca[5,6], Darryl C. De Vivo, MD[1,5], Michele Caggana, ScD, FACMG[3] and Wendy K. Chung, MD, PhD[1,7]

Status of NBS for SMA in Europe and USA

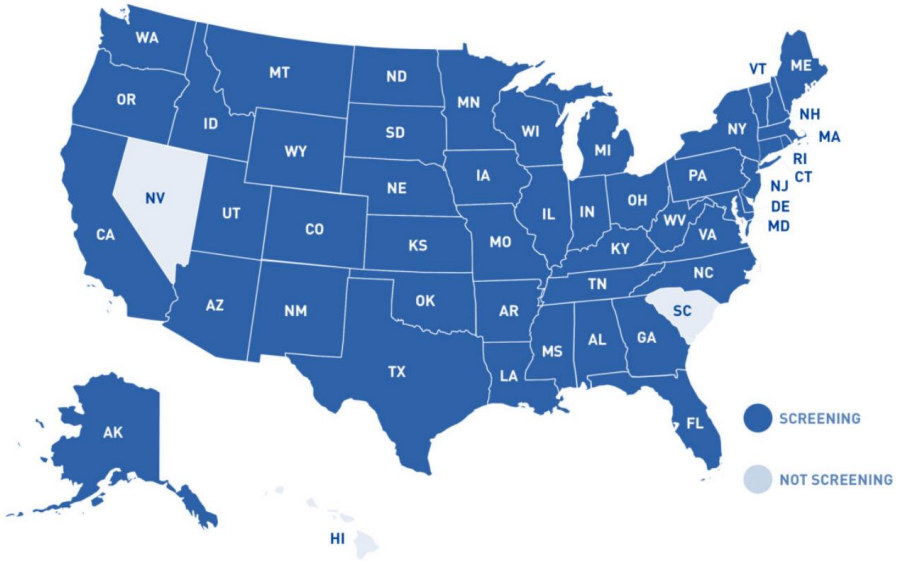
Europe



- Currently screening all infants for SMA
- SMA approved for NBS panel, **ongoing** implementation
- SMA approved for NBS panel, **pending** implementation
- Application for national program submitted
- Active pilot
- Stakeholders engaged to consider adding SMA to the NBS panel
- No activity at present

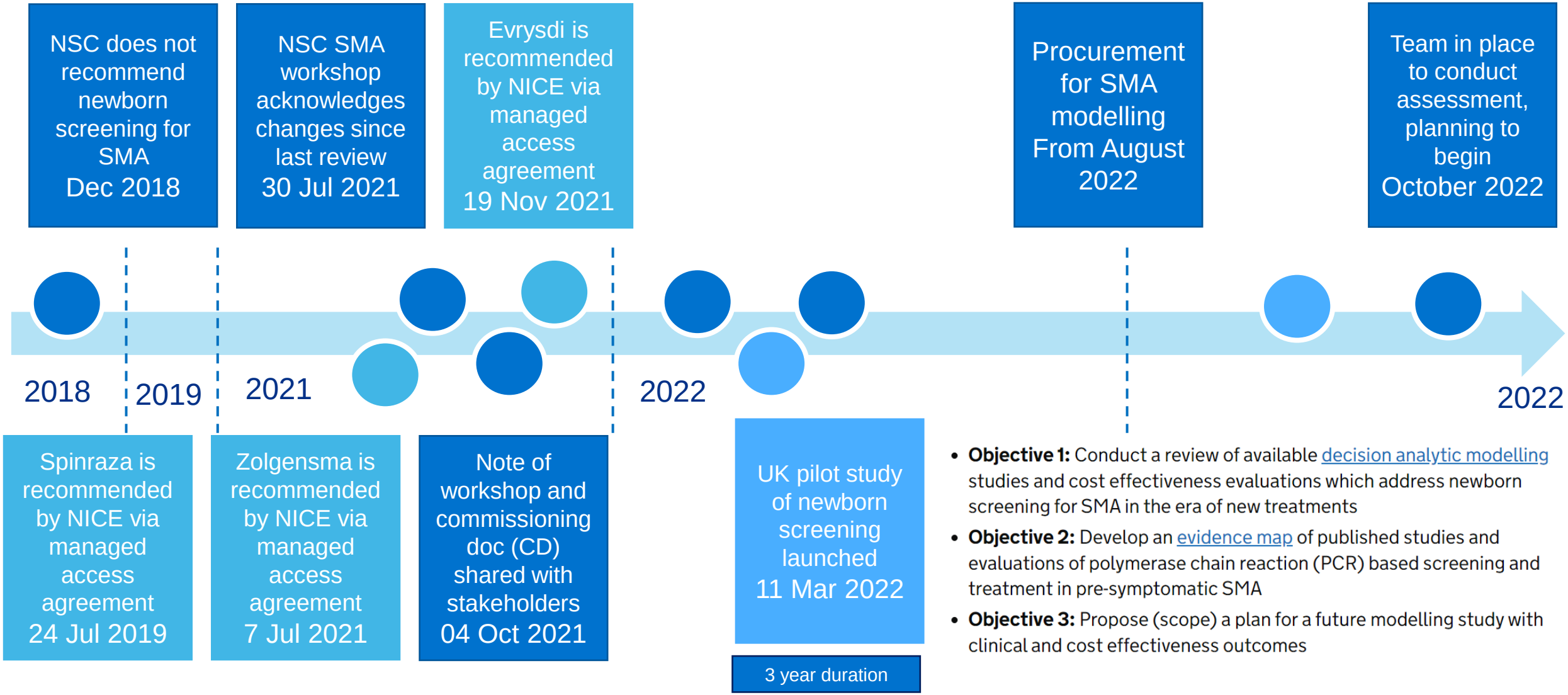
United States

As of August 2022, 47/50 states are currently screening all infants for SMA



Date: 6 September 2022. We are only sharing details about NVS-supported pilots.

A timeline of recent and expected events (England)



- **Objective 1:** Conduct a review of available decision analytic modelling studies and cost effectiveness evaluations which address newborn screening for SMA in the era of new treatments
- **Objective 2:** Develop an evidence map of published studies and evaluations of polymerase chain reaction (PCR) based screening and treatment in pre-symptomatic SMA
- **Objective 3:** Propose (scope) a plan for a future modelling study with clinical and cost effectiveness outcomes

University of Oxford Pilot study

Population-based newborn screening for spinal muscular atrophy to evaluate acceptability and feasibility of screening in the UK context

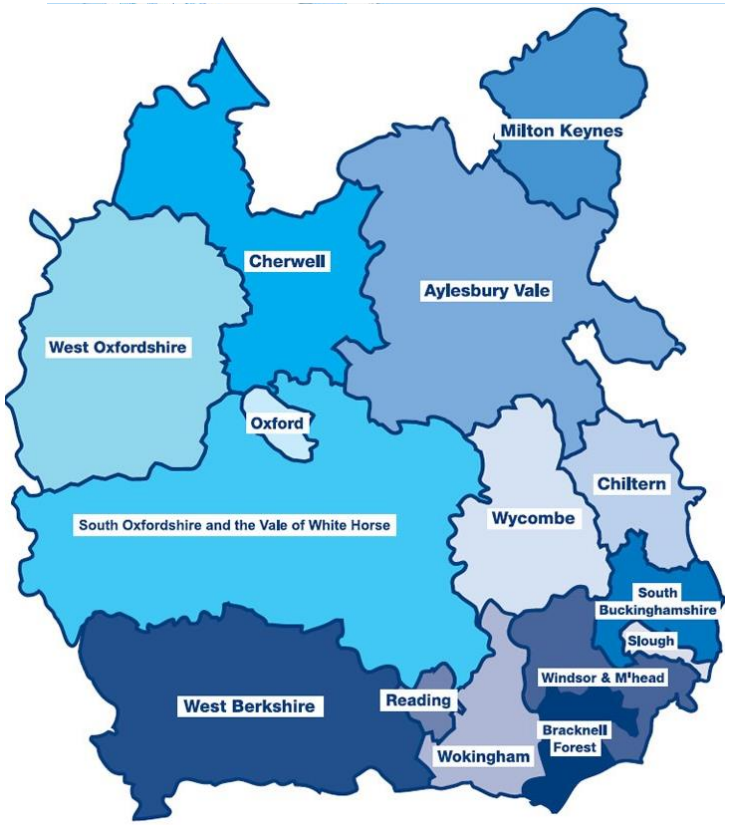
Primary objective

- Uptake of newborn bloodspot genetic screening for SMA

Secondary objectives

- Feasibility and reliability of identifying true positive cases
- Feasibility and reliability of identifying true negative cases
- Feasibility of performing SMA screening on newborn dried blood spot
- Epidemiology of SMA in the Thames Valley

University of Oxford Pilot study



- Recruitment began 11th March 2022
- Mother ≥18 weeks' gestation, up until 28 days post-natally.
- Participating Thames Valley hospitals
  - John Radcliffe Hospital
  - Horton General Hospital
  - Milton Keynes University Hospital
  - Stoke Mandeville Hospital
  - Royal Berkshire Hospital
  - Wycombe general hospital
- Minimum 10,000 newborns per year over the course of 3 years

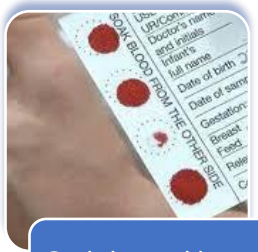
SMA-NBS Pilot Workflow – Oxford

UNIVERSITY OF OXFORD

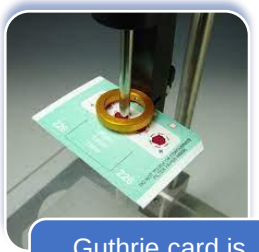
Mother approached at antenatal appointment or on postnatal ward

Midwife attains eConsent

Routine bloodspot is collected on Guthrie card at day 5

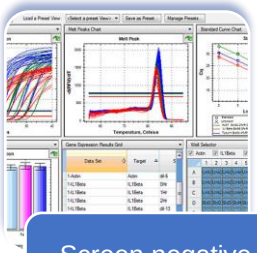


Guthrie card is sent to NHS Screening Laboratory at the John Radcliffe

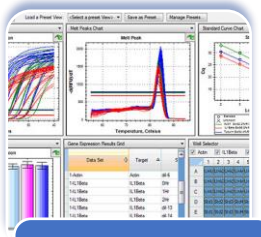


Guthrie card is flagged and bloodspot collected for SMA test (3.2mm punch)

Bloodspot sent to NHS Oxford Regional Genetics lab where DNA is extracted and qPCR performed



Screen negative results reported to parents 4 weeks after test performed



Screen positive result- MLPA test performed and family contacted

Blood sample collected and sent for MLPA at independent site

DNA, deoxyribonucleic acid; MLPA, multiplex litigation-dependent probe amplification; NBS, newborn screening; NHS, National Health Service; SMA, spinal muscular atrophy; qPCR, quantitative polymerase chain reaction.

Update – 7th November 2022

- Consented 4,446 mums
- 2613 results

- Full dataset
  - Mean age at reporting = 21.7 days
  - Mean TAT from DBS receipt to report = 14.6 days

- Data for most recent 500 reports
  - Mean age at reporting = 13.3 days
  - Mean TAT from DBS receipt to report = 6.2 days

CHALLENGE

43 patients identified

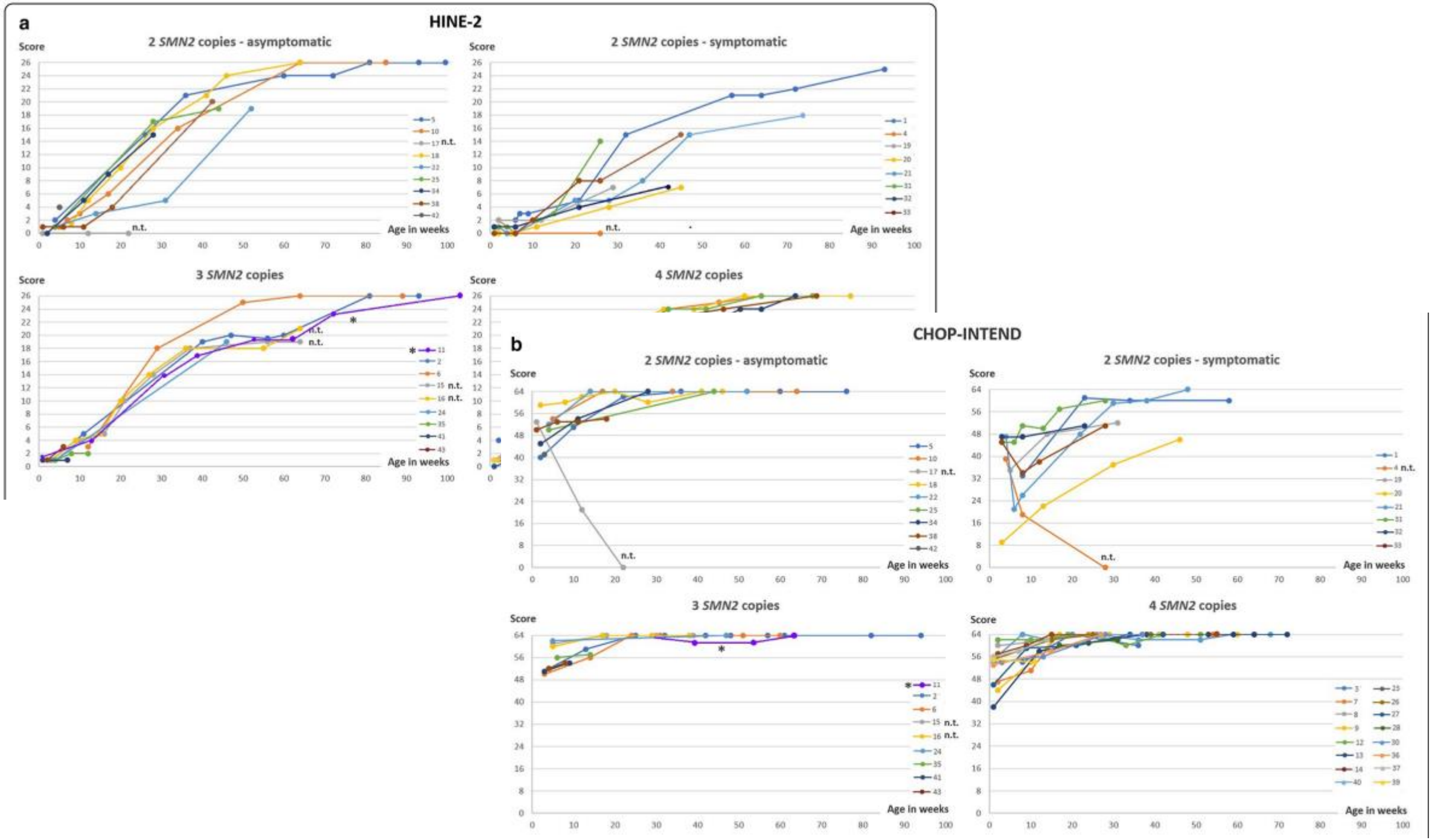
2 SMN2 copies -17(39.5%)
3 SMN2 copies – 10 (23%)
4 SMN2 copies – 14 (32.5%)
5 SMN2 copies – 2 (4.5%)

RESEARCH Open Access

Newborn screening for spinal muscular atrophy in Germany: clinical results after 2 years

Katharina Vill[1†], Oliver Schwartz[2†], Astrid Blaschek[1], Dieter Gläser[3], Uta Nennstiel[4], Brunhilde Wirth[5], Siegfried Burggraf[6], Wulf Röschinger[6], Marc Becker[6], Ludwig Czibere[6], Jürgen Durner[6,7], Katja Eggermann[8], Bernhard Olgemöller[9], Erik Harms[10], Ulrike Schara[11], Heike Kölbel[11†] and Wolfgang Müller-Felber[1*†]

- Eight patients with 2 SMN2 copies had early signs SMA
- Asymptomatic (examination and ulnar CMAP >1)– 9 (2 SMN2 copies) and all patients with 3 or more SMN2


a
HINE-2
2 SMN2 copies - asymptomatic
2 SMN2 copies - symptomatic
3 SMN2 copies
4 SMN2 copies
Score
Age in weeks
n.t.
b
CHOP-INTEND
2 SMN2 copies - asymptomatic
2 SMN2 copies - symptomatic
3 SMN2 copies
4 SMN2 copies
Score
Age in weeks
n.t.

Three years pilot of spinal muscular atrophy newborn screening turned into official program in Southern Belgium

François Boemer[1], Jean-Hubert Caberg[2], Pablo Beckers[1], Vinciane Dideberg[2], Samantha di Fiore[1], Vincent Bours[3], Sandrine Marie[4], Joseph Dewulf[4], Lionel Marcelis[5], Nicolas Deconinck[6], Aurore Daron[7], Laura Blasco-Perez[8], Eduardo Tizzano[8], Mickaël Hiligsmann[9], Jacques Lombet[10], Tatiana Pereira[10], Lucia Lopez-Granados[10], Sarvnaz Shalchian-Tehran[11], Véronique van Assche[12], Arabelle Willems[12], Sofie Huybrechts[13], Bénédicte Mast[14], Rudolf van Olden[15], Tamara Dangouloff[7] & Laurent Servais[7,16]

9 patients identified
2 SMN2 copies – 4
3 SMN2 copies – 3
4 SMN 2 copies- 2

At first assessment :

- All patients with 2 copies of SMN 2 had clinical signs of SMA (hypotonia and or areflexia)
- All patients with 3 and 4 copies were asymptomatic

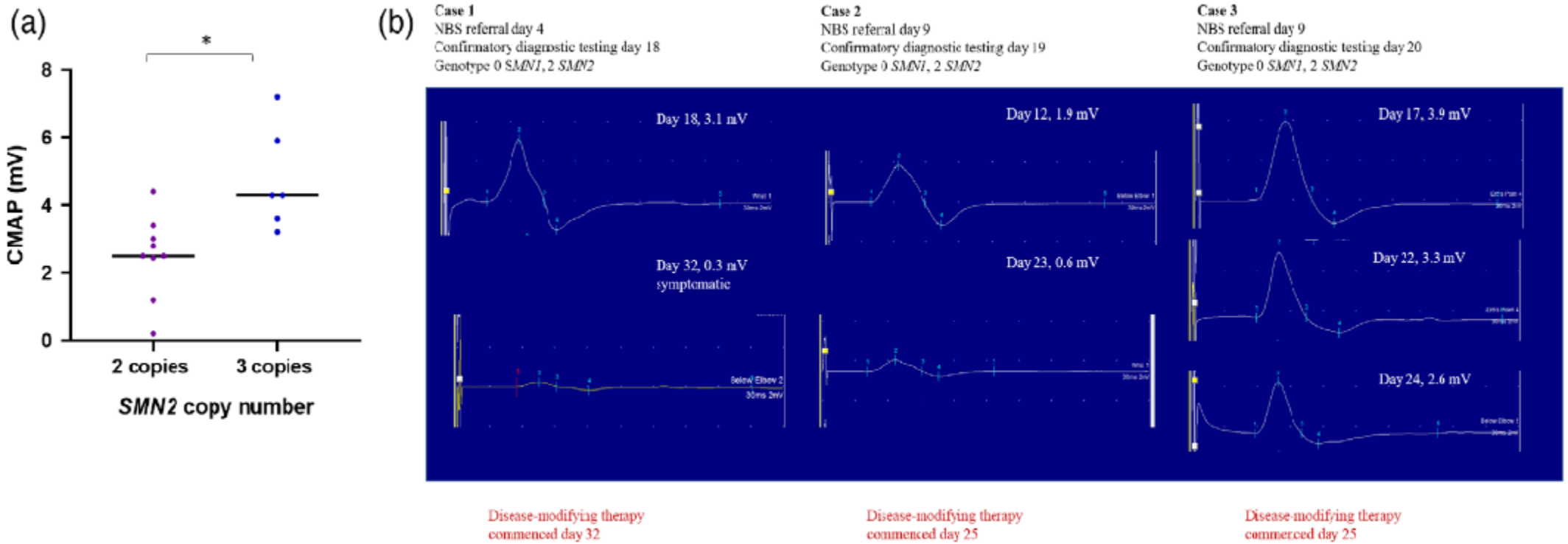
Integrating newborn screening for spinal muscular atrophy into health care systems: an Australian pilot programme

ARLENE M D'SILVA[1,2] | DIDU S T KARIYAWASAM[1,2] | STEPHANIE BEST[3,4] | VERONICA WILEY[5,6] | MICHELLE A FARRAR[1,2] | NSW SMA NBS STUDY GROUP*

21 patients identified

2 SMN2 copies – 12
3 SMN2 copies – 8
4 SMN 2 copies- 1

6 (28%) were symptomatic by 4 weeks


(a)
*
CMAP (mV)
8
6
4
2
0
2 copies
3 copies
SMN2 copy number
(b)
Case 1
NBS referral day 4
Confirmatory diagnostic testing day 18
Genotype 0 SMN1, 2 SMN2
Case 2
NBS referral day 9
Confirmatory diagnostic testing day 19
Genotype 0 SMN1, 2 SMN2
Case 3
NBS referral day 9
Confirmatory diagnostic testing day 20
Genotype 0 SMN1, 2 SMN2
Day 18, 3.1 mV
Day 12, 1.9 mV
Day 17, 3.9 mV
Day 32, 0.3 mV
symptomatic
Day 23, 0.6 mV
Day 22, 3.3 mV
Day 24, 2.6 mV
Disease-modifying therapy
commenced day 32
Disease-modifying therapy
commenced day 25
Disease-modifying therapy
commenced day 25

Can we accurately predict the outcome for infants identified by newborn screening?

SMN copy numbers

- Not all patients are asymptomatic

  - 50% patients with 2 SMN2 copied are symptomatic even when identified NBS

- Early treatment

  - 3 or more copies of SMN2 >90% within normal developmental milestones

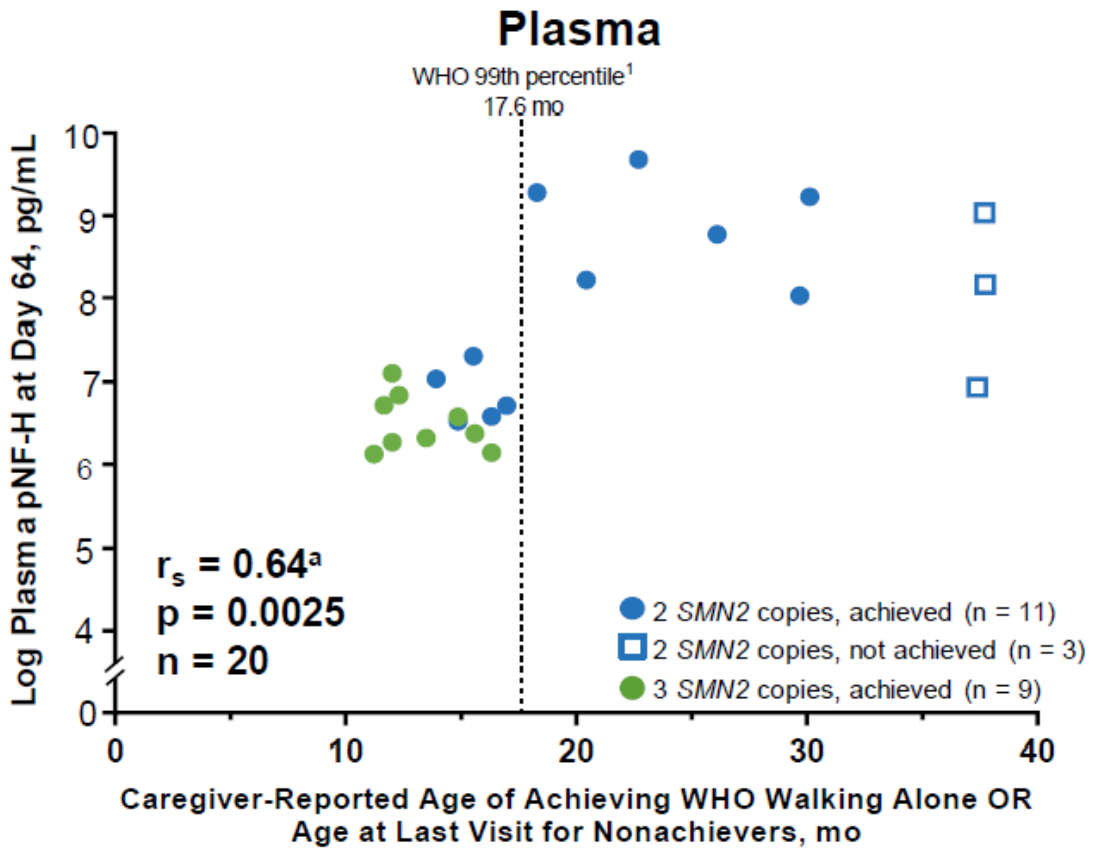
  - 2 copies around 50% within normal developmental milestones

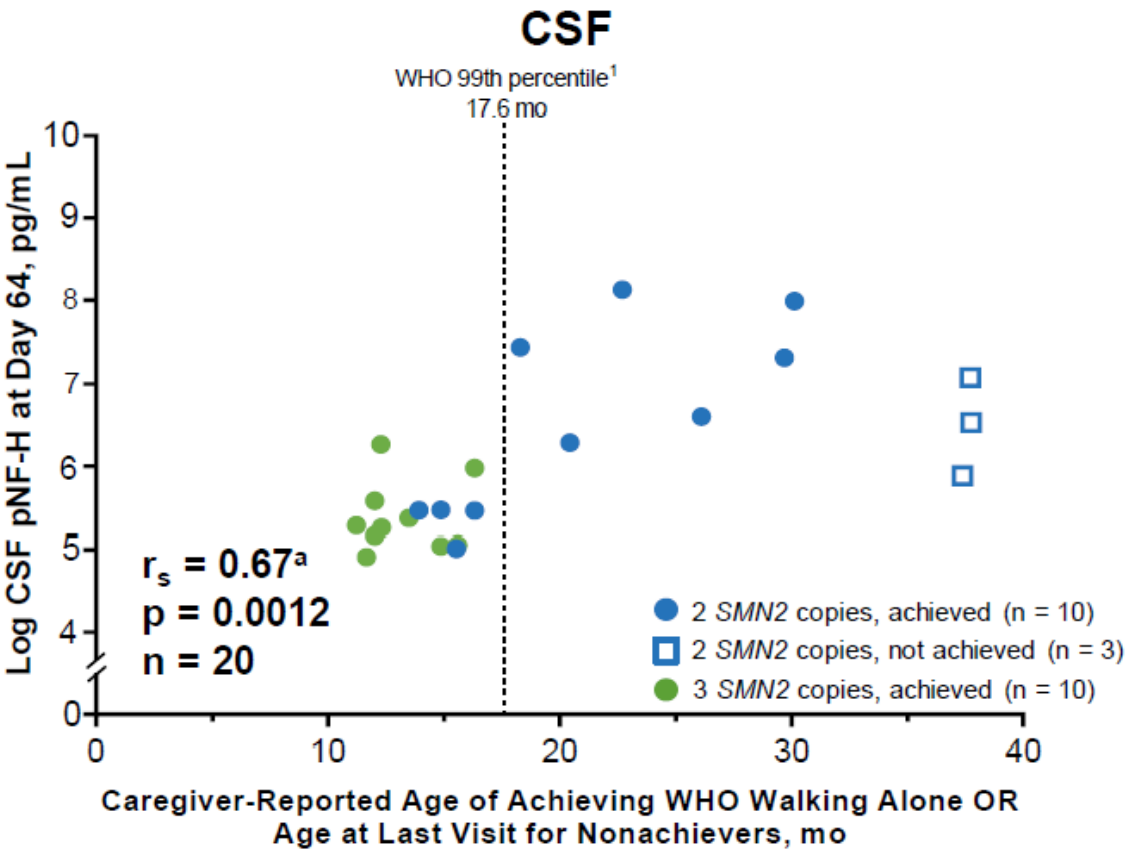
Treatment

NICE Managed Access Agreement – Inclusion criteria

Nusinersen (Spinraza)	Onasemnogene abeparvovec (Zolgensma)	Risdiplam (Evrysdi)
Children who have SMA Type 1, 2 or 3 who: • are not permanently ventilated for more than 16 hours a day/ tracheostomy • Safely deliver LP No other treatment **Pre-symptomatic and have 1 to 4 *SMN2* copies**	Children who have SMA Type 1 who: • are below a weight of 21kg • AAV 9 titre < 1:50 • do not have any other risk factors (e.g., liver disease) If a child is receiving another treatment, this will stop **Pre-symptomatic and have up to 3 *SMN2* copies**	Children who have SMA Type 1, 2 or 3 who: • are over 2 months of age • are not permanently ventilated for more than 16 hours a day/tracheostomy No other treatment **Pre-symptomatic and have 1 to 4 *SMN2* copies**

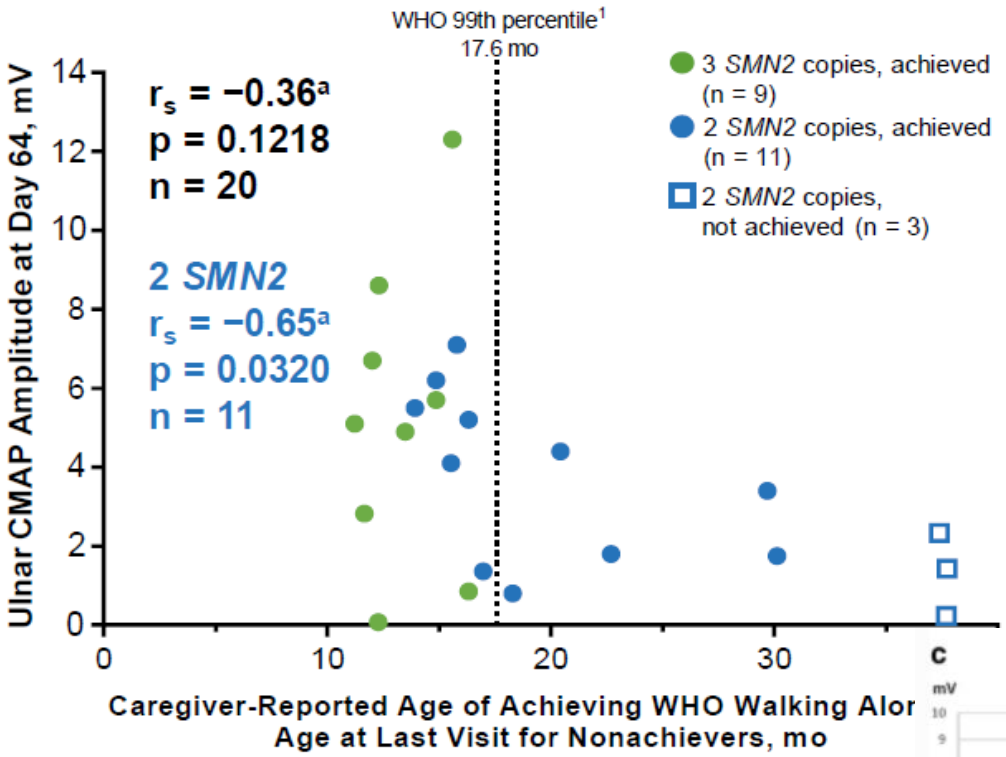
Neurofilament

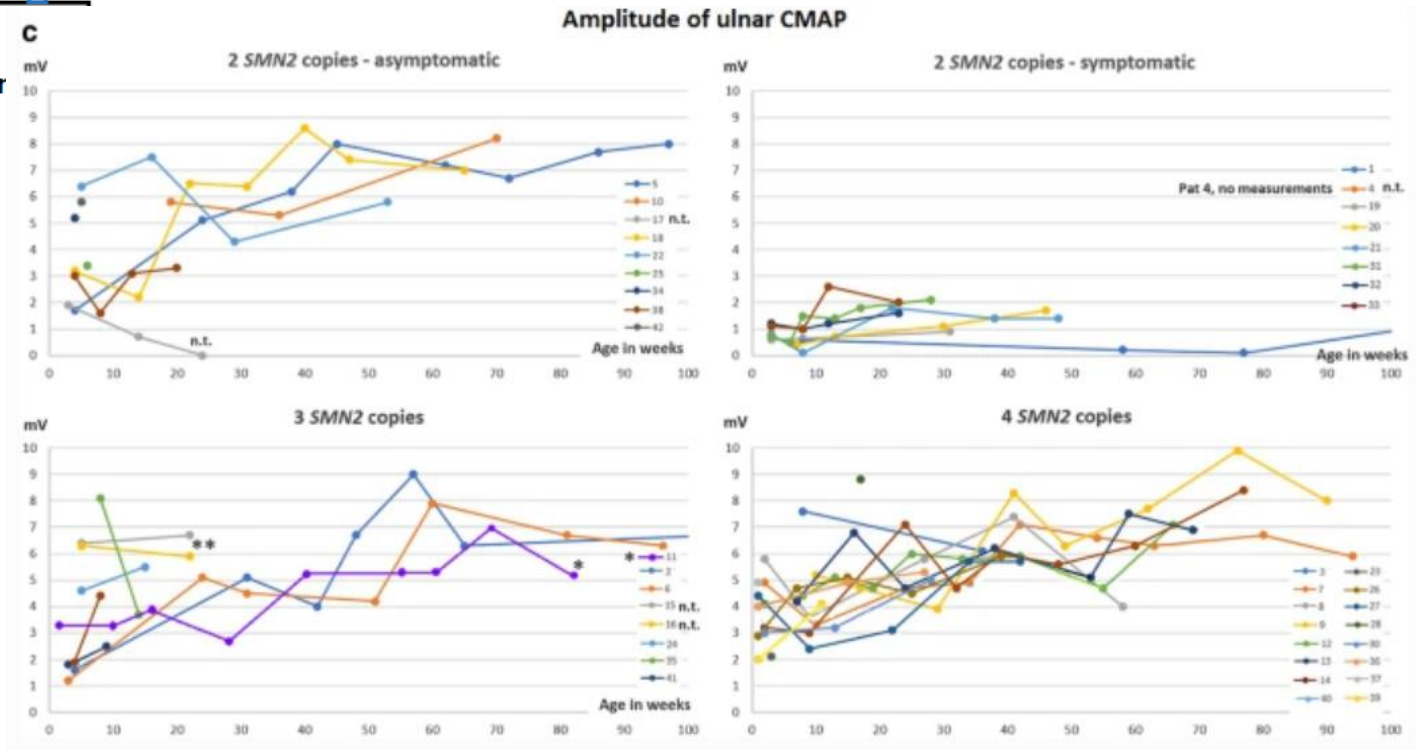




Nuturestudy data- ICNMD 2021

CMAP

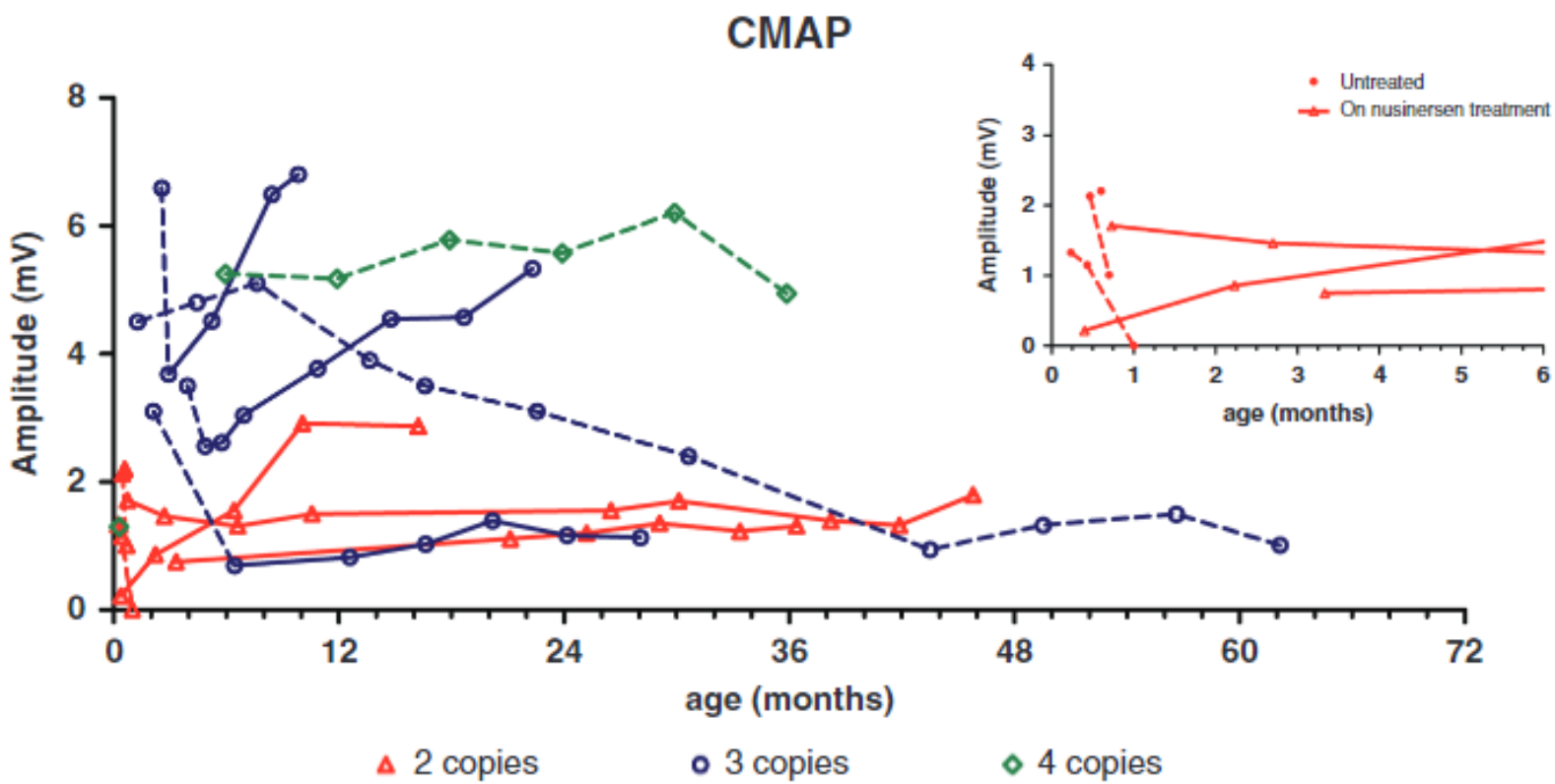




Nuture study data - ICNMD 2021
Villi K et al- Orph J Rare Dis 2021

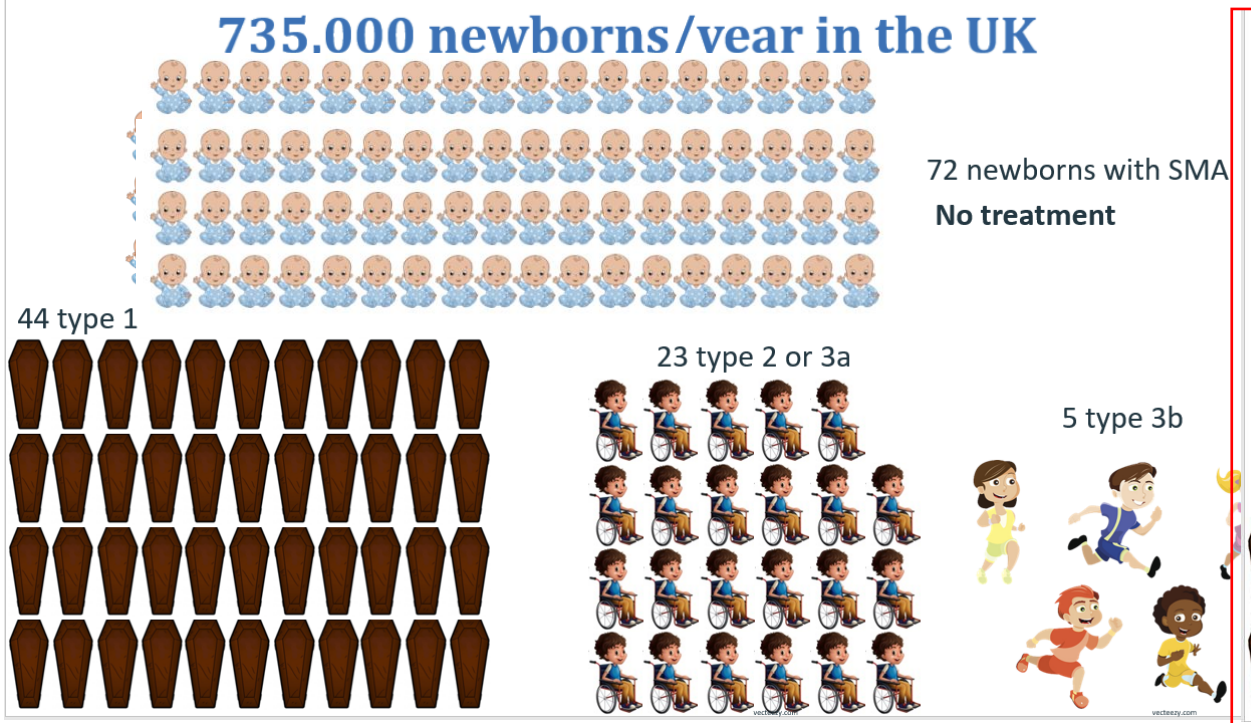
CMAP changes upon symptom onset and during treatment in spinal muscular atrophy patients: lessons learned from newborn screening

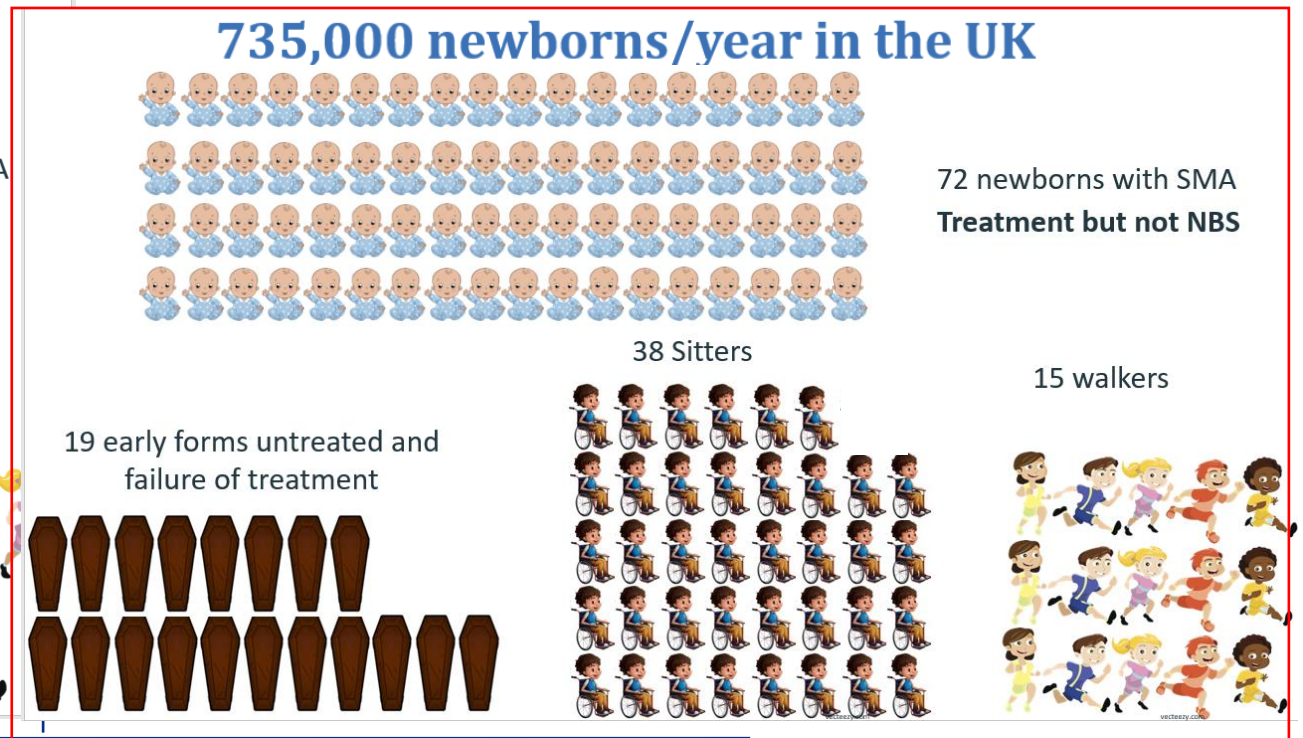
Wen-Chin Weng, MD, PhD[1,2], Yu-Kan Hsu, MD[1], Fu-Man Chang, MD[3], Chun-Yen Lin, MD, MS[4], Wuh-Liang Hwu, MD, PhD[1,2,5], Wang-Tso Lee, MD, PhD[1,2], Ni-Chung Lee, MD, PhD[1,2,5] and Yin-Hsiu Chien, MD, PhD[1,2,5]

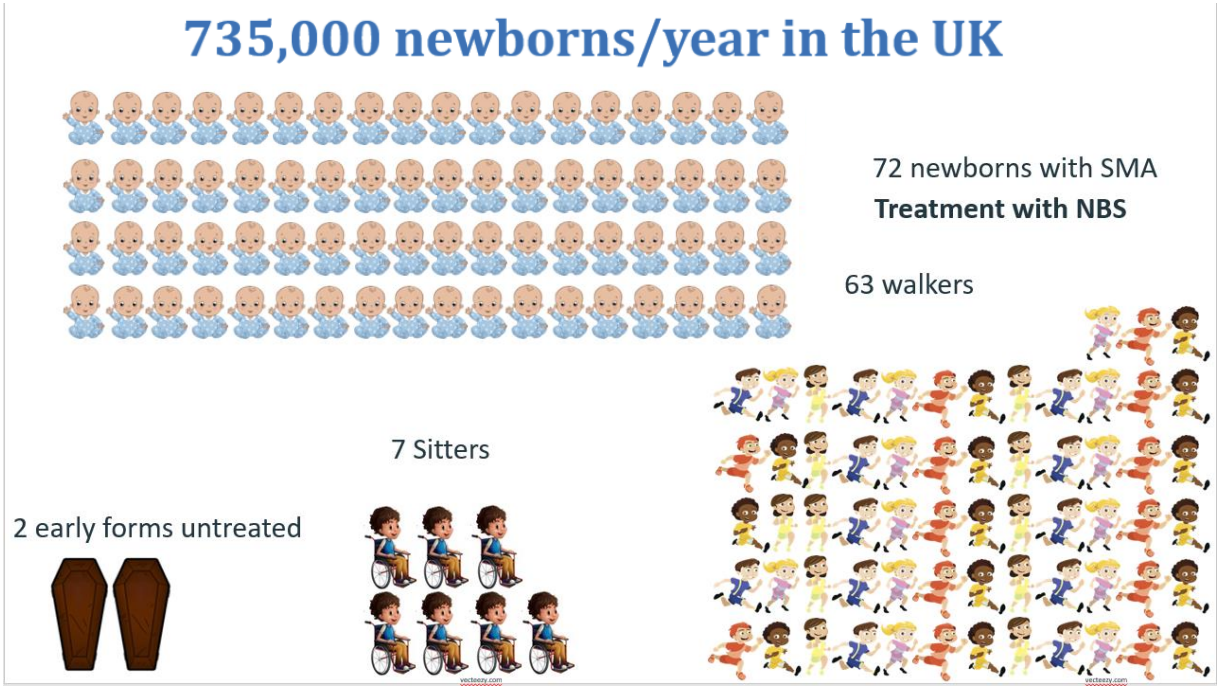


Challenges : Cost of the disease Vs the cost of screening

- Cost-effectiveness of newborn screening of SMA
- Compared the cost of the disease in addition to treatment Vs the cost of the screening in addition to treatment







- Current medical costs

SMA1 : $ 75,047 - 196,429/year

SMA 2-4 : $27,157 - 82,474/year

Summary – SMA newborn screening programme

- Critical to achieving best clinical outcomes for patients from SMA treatments.
- Are effective with low false positive and false negative cases.
- Are cost effective in the long term.
- Patients identified by NBS must be treated urgently.
- Improved biomarkers are required to counsel families on long-term outcomes

Thank you and questions

NBS team at the Oxford

Prof Laurent Servais

Prof Manu Vatish

Dr Gemma Fisher

Dr Carl Fratter

Corinne Betts

Arabella Volkers

All the midwives