5th
International Scientific Congress on
Spinal Muscular Atrophy

BUDAPEST

11th — 14th March 2026

ABSTRACT BOOK

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Welcome

SMA Europe takes great pride in inviting you to the 5th International Scientific Congress on Spinal Muscular Atrophy (SMA), from 11th to 14th March 2026 in Budapest, Hungary. Our Congress is the largest scientific congress dedicated to SMA and brings together scientists and young researchers as well as clinicians and other health-care professionals from all over the world.

SMA Europe is a non-profit umbrella organisation of SMA patient organisations from across Europe. We work together to create a better world for all those living with SMA. One of our core activities is to foster patient-relevant research in the field of SMA, to communicate the value generated from research, and, consequently, to ensure future support for research within our community.

The goal of our scientific congress is to bring together an international and multidisciplinary group of scientists and health-care professionals. We provide a venue to present and exchange breakthrough ideas relating to SMA, especially also in light of the patient-relevance of their findings, and to cement existing and stimulate new collaborations.

Equally, our congress is a platform for talented young researchers. Together with experienced scientists, health-care professionals, and patient experts, they will discuss, debate and dissect significant new developments and advancements related to SMA. Moreover, they will share their visions for the future of SMA research by providing an opportunity to exchange scientific evidence and clinical experiences. Therefore, we trust that the conference will lead to ever-improved treatment and care for patients living with SMA.

All together. One Goal.

Yasemin Erbas
President, SMA Europe

Nicole Gusset
CEO, SMA Europe

SMA
EUR
OPE

About us

SMA Europe is a non-profit umbrella organisation of spinal muscular atrophy (SMA) patient organisations from across Europe. We work to bring effective treatments and optimal care to everyone living with SMA.

Together, through greater understanding, we will create a better world for all those living with SMA.

All together. One goal.

Our priorities

Research

Our mission is to be active and progressive in the search for treatments for SMA. We do this through promoting and generating patient-relevant data. We are supported by a Scientific Advisory Board (SAB), composed of neuroscientists and neurologists with particular expertise in SMA.

Through our research programme, we:

- Seek to set patient-relevant research priorities
- Promote these patient-relevant research priorities in our Call for Research Proposals and our scientific congresses
- Systematically research and assess the needs and wants of people living with SMA
- Identify data gaps that are relevant to patients and fill those by:
    - producing our own patient-relevant research projects and publishing the outcome in peer-reviewed journal
    - stimulating, (collaboratively) supporting and funding research that addresses these gaps
    - facilitating communication between stakeholders in this field.

We also build our members' capacity to understand the relevance and processes of research, to allow them to become partners in funding research and in meaningfully contributing to discussions and solutions. In so doing, we make sure SMA research delivers on patients' unmet needs from a clinical, care and quality of life perspective.

We do this because we believe that developing a treatment that can truly help improve the lives of people living with SMA should be rooted in a firm understanding of the challenges those people face in their daily lives, their needs and the trade-offs they are willing to make to gain relief.

To ensure the creation of valuable treatments, all aspects of the health care system, including research prioritisation, product development, trial design, regulatory approval, access, reimbursement and treatment decisions, will need to align with their needs.

Therapy and Care

SMA Europe strives to accelerate progress in the diagnosis, treatment and care of people with SMA.

To this aim, we engage in dialogue with all relevant stakeholders, to ensure the needs and wants of people living with SMA across Europe are taken into account during the entire drug development process.

To justify a seat at all relevant tables and to be able to provide meaningful, qualified and evidence-based input, SMA Europe continuously educates and prepares individual patient advocates in key knowledge areas. In parallel, SMA Europe strives to collaborate with all key stakeholders as a respected partner, especially in the areas of drug development and regulatory affairs.

Healthcare Systems, Policy and Access

Access to diagnosis, treatment and care is fragmented in Europe. SMA Europe strives for unrestricted access to optimal available medicine, treatment, care and diagnostics, regardless of location, age, mobility or SMA type. This is the only outcome which will end the access inequalities that SMA families continue to live with today.

We address this issue by mapping and centralising information around access throughout Europe. We identify data gaps that influence access and we promote research to fill them. We support our members by sharing knowledge and coaching them to advocate efficiently in their own country. At a European level, we partner with and influence all stakeholders in relevant areas of healthcare and research, wherever impact can be made, bearing in mind that responsibilities in access tend to fall at national level and are limited at European level.

SMA EUROPE Member Organisations

Austria
SMA Österreich
www.smaoesterreich.at

Belgium
SMA Belgium
www.spierziektenvlaanderen.be
www.telethon.be

Cyprus
MDA Cyprus
www.mdacyprus.org

Czech Republic
SMÁci
www.smaci.cz

Denmark
Muskelsvindfonden
www.muskelsvindfonden.dk

Finland
SMA Finland
www.smafinland.fi

France
AFM-Téléthon
www.afm-telethon.fr

Germany
DGM/Initiative SMA
www.dgm.org
www.initiative-sma.de

Greece
MDA
www.mdahellas.gr

Hungary
SMA Hungary
www.smahun.hu

Iceland
FSMA Iceland
www.fsma.is

Ireland
SMA Ireland
www.smaireland.com

Israel
Families of SMA Israel
www.sma.org.il

Italy
Famiglie SMA
www.famigliesma.org

The Netherlands
Prinses Beatrix Spierfonds
www.prinsesbeatrixspierfonds.nl

The Netherlands
VSN - Spierziekten Nederland
www.spierziekten.nl

North Macedonia
Stop SMA
www.stopsma.mk

Poland
Fundacja SMA
www.fsma.pl

Portugal
APN
www.apn.pt

Romania
Asociatia SMACARE
www.amiotrofie-spinala.ro

Russia
SMA Family Foundation Russia
www.f-sma.ru

Serbia
SMA Serbia
www.smasrbija.rs/en/support

Slovakia
SMA Slovakia
www.sma-slovakia.sk

Spain
FundAME
www.fundame.net

Sweden
NSMA
www.nsma.nu

Switzerland
SMA Schweiz
www.sma-schweiz.ch

Turkey
SMA Benimle Yürü
www.smabenimleyuru.org.tr
www.sma.org.tr

Ukraine
CSMA
www.csma.org.ua

United Kingdom
SMA UK
www.smauk.org.uk

PROGRAMME

WEDNESDAY 11TH MARCH 2026

08.30 - 12.45

Global SMAdvocacy Event — Liszt I-III
(by invitation only)

12.30 - 14.00

Registration

14.00 - 15.30

Workshops (running in parallel) - see page 303

Workshop 1 — Bartók II
Assessing fatigability in Spinal Muscular Atrophy: Exploring the contribution of neuromuscular junction dysfunction
Organised by the Industry & Karen Chen, SMA Foundation New York, USA

Workshop 2 — Liszt I-III
Beyond boundaries: Elevating SMA care for the future
Organised by the Industry

Workshop 3 — Lehar I-III
Old signals, new insights: Electrophysiology as a biomarker in SMA
Organised by Kathryn Swoboda, Massachusetts General Hospital, Boston, USA & Renske Wadman, UMC Utrecht, The Netherlands

Workshop 4 — Bartók I
MAPS - Mobility, Activity, Play, and Sports
Organised by José Longatto, Great Ormond Street Hospital, London, UK

Workshop 5
Respiratory care in SMA — Brahms I
Organised by Esther Veldhoen, UMC Utrecht, The Netherlands & Lisa Edel, Great Ormond Street Hospital, London, UK

Workshop 6 — Mozart I-III
Nutritional management in SMA in the new treatment era: From fundamental science to clinical practice
Organised by Simona Bertoli, IRCCS Istituto Auxologico Italiano, Milan, Italy

15.30 - 16.00

Coffee Break

16.00 - 17.30

Workshops (running in parallel) -see page 311

Workshop 7 Bartók II

Every motor neuron matters - Biomarkers and treatment choice in SMA

Organised by the Industry & Eduardo Tizzano, Vall D'hebron Research Institute (VHIR), Barcelona, Spain

Workshop 8 Liszt I-III

Contractures in SMA: From scientific insights to therapeutic targets

Organised by FundAME, Madrid, Spain

Workshop 9 Mozart I-III

Addressing unmet Needs in SMA care through multidisciplinary collaboration and education

Organised by the Industry

Workshop 10 Bartók I

The role of early parental empowerment in management of emergencies and urgencies at home in pharmacologically treated SMA type 1

Organised by Chiara Mastella, SAPRE-UONPIA, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico Milan, Italy

Workshop 11 Lehar I-III

SMA and neurodevelopmental disorders: A call for harmonized strategies

Organised by Giovanni Baranello, UCL Great Ormond Street Institute of Child Health, London, UK

Workshop 12 Brahms I-II

Bench to bedside and back - Fundamental discoveries in connection with patient journeys

Organised by Ewout Groen, UMC Utrecht, The Netherlands

17.30 - 19.30

Welcome Reception and Opening Activity (light refreshments)

THURSDAY 12TH MARCH 2026

08.00 - 10.00 Registration & Welcome Coffee

10.00 - 10.30 **Welcome and Opening Talk** — Pàtria Hall
Tom Gillingwater, Chair Scientific Advisory Board SMA Europe
Yasemin Erbas, President SMA Europe
Nicole Gusset, CEO SMA Europe

10.30 - 12.15 Session 1: Biomarkers in SMA
Chair: Ewout Groen UMC Utrecht, The Netherlands

O1 **Defining and refining biomarkers in Spinal Muscular Atrophy**
Keynote Speaker: Ewout Groen, UMC Utrecht, The Netherlands

O2 **Muscle-specific extracellular vesicles: A novel biomarker for Spinal Muscular Atrophy**
Melissa Bowerman, Keele University, UK

O3 **Therapeutic and biomolecular effects of long-term nusinersen treatment in 5q Spinal Muscular Atrophy type 2 and 3: A long-term CSF proteomic study**
Gina Cebulla, Heidelberg University Hospital, Germany

O4 **Motor unit patterns correlate with severity in symptomatic patients with Spinal Muscular Atrophy**
Renske Wadman, UMC Utrecht, The Netherlands

O5 **Multi-omic Biomarkers for personalized Spinal Muscular Atrophy management: A multicenter Italian study**
Stefania Corti, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Italy

O6 **Titin and the muscle-brain axis in SMA: A promising biomarker for Nusinersen therapy across CSF transcriptome and radiological perspective**
Francesca Dragoni, IRCCS Mondino Foundation, Italy

12.30 - 14.00 Lunch Break

13.00 - 13.45 **Industry Sponsored Session** - see page 318 — Pàtria Hall
(Patient advocates not admitted due to local compliance regulations)

13.00 - 13.45 **Advocates session:** — Bartók II
"The need for basic research in SMA: A discussion between advocates and researchers."
Chairs: Marie-Christine Ouillade, Cécile Martinat.
(Patient advocates only)

14.00 - 15.45

Session 2: Regeneration and disease modifiers — Pàtria Hall

Chair: Linda Greensmith, University College London, UK

O7 **A novel optogenetic cell therapy approach to restore muscle innervation in ALS**
Keynote speaker: Linda Greensmith, University College London, UK

O8 **Biomimetic viscoelastic hydrogels promote motor neuron outgrowth and modulate Astrocyte behaviour for Spinal Muscular Atrophy regeneration applications**
Cian O'Connor, Harvard University and Royal College of Surgeons in Ireland, Ireland

O9 **Neuromuscular organoids reveal developmental transcriptomic dysregulation in SMA**
Morgan Gazzola, I-Stem, Corbeil-Essonnes, France

O10 **A novel mouse model of X-linked Spinal Muscular Atrophy offers a platform for preclinical development of UBA1 targeting therapeutics**
Hannah Crick, University of Edinburgh, UK

O11 **Primary cortical neuron cultures as a novel reliable in vitro model to test treatment efficacy for spinal muscular atrophy**
Serena Stanga, Neuroscience Institute Cavalieri Ottolenghi, University of Turin, Italy

O12 **Significant microvascular pathology is driven by specific SMN depletion in endothelial cells: The 'EndoSMA' mouse**
Alaa Alshwayyat, University of Aberdeen, UK

15.45 - 16.15

Flash Poster Presentations — Pàtria Hall

P170 **Proteomic profiling of cytoplasmic stress-induced liquid condensates of SMN**
Yannick Riedel, Institute of Genetics, University of Bonn, Germany

P126 **Exploring the trajectory of swallowing within psychomotor development in Spinal Muscular Atrophy: Moving toward integrated care**
Sofia Gandolfi, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

P204 **5q-SMA emergency management support tool: Collaborative construction of an emergency card**
Aline Giuliani, Viva Iris, Uberlândia, Brazil

P206 **Polysomnographic findings in children with Spinal Muscular Atrophy**
Milena Villamil, Osorio Fundación Hospital Pediátrico la Misericordia, Bogotá, Colombia

P18 **Prenatal SMN-dependent defects in translation uncover reversible primary cilia phenotypes in SMA**
Helena Chaytow, University of Edinburgh, UK

P196 **Posttranslational regulation of the Survival Motor Neuron (SMN) complex**
Claudia Cobos, University of Vienna, Institute of Biological Chemistry, Austria

16.15 - 16.45 Coffee Break & Poster Session

16.15 - 17.30 **Poster Session 1** — Gallery Level
Chair: Tom Gillingwater, University of Edinburgh, UK

17.30 - 18.15 **Industry Sponsored Session - see page 319** — Pàtria Hall
(Patient advocates not admitted due to local compliance regulations)

Advocates session: — Bartók II
"Working with industry: What really happens, and where advocates can make a difference"
Chairs: Nicole Gusset, Friedrich Metzger.
(Patient advocates only)

19.30 - 22.00 Thank You Dinner (by invitation only)

FRIDAY 13TH MARCH 2026

08.00 - 08.45 — **Industry Sponsored Session - see page 320** — **Pàtria Hall**
(Patient advocates not admitted due to local compliance regulations)

08.00 - 08.45 — **Advocates session:** — **Bartók II**
"Global access to diagnosis, treatment, and care: A conversation with advocates and physicians."
Chairs: Yasemin Erbas, Giovanni Baranello.
(Patient advocates only)

09.00 - 10.30 — **Session 3: Metabolism and diet in SMA** — **Pàtria Hall**
Chair: Alessandro, Usiello, University of Campania "Luigi Vanvitelli", Italy

O13 **Mitochondrial dysfunction in Spinal Muscular Atrophy: Emerging insights from disease mechanisms to therapeutic targets**
Camilla Bean, UniCamillus, Rome, Italy

O14 **Adipokines in adult patients with Spinal Muscular Atrophy Type 3: Challenging the canonical narrative**
Marija Miletic, University Clinical Center of Serbia, Serbia

O15 **Oxidative stress in Spinal Muscular Atrophy (SMA): Cellular mechanisms and antioxidant therapeutic potential**
Phoebe Rassinoux, INMG-PGNM, Lyon, France

O16 **Mitochondrial and redox perturbations in SMA: Insights from multi organ omics and therapeutic targeting of the NRF2-KEAP1 Axis**
Sofia Vrettou, Center for Molecular Medicine, University of Cologne, Germany

O17 **SMN protein levels impact the metabolism of neuroactive amino acids in preclinical models and SMA patients**
Keynote Speaker: Alessandro Usiello, University of Campania "Luigi Vanvitelli", Italy

10.30 - 11.00 — Coffee Break

11.00 - 12.30 — **Session 4: Sensorimotor function and fatiguability in SMA**
Chair: George Mentis, Columbia University, New York, USA

O18 **Sensory-motor neuronal dysfunction: An essential pathomechanism in animal models and patients of SMA**
Keynote Speaker: George Mentis, Columbia University, New York, USA

O19 **Cortical GABAergic dysregulation and metabolic alterations in a Spinal Muscular Atrophy mouse model**
Giovanna Menduti,Neuroscience Institute Cavalieri Ottolenghi, University of Turin, Italy

O20 **Advancing assessment of perceived physical fatigability using the SMA EFFORT**
Rafael Rodriguez-Torres, Columbia University Irving Medical Center, USA

O21 **smn-1 regulates motoneurons and dopaminergic neurons crosstalk in C. elegans**
Giada Onorato, Institute of Biosciences and BioResources, CNR, Naples, Italy

O22 **Motor neuron pathology drives spinal circuit defects and phenotype of Spinal Muscular Atrophy with respiratory distress type 1**
Gabriel Kohn, Carl-Ludwig-Institute for Physiology, Leipzig University, Germany

12.30 - 14.00 Lunch Break

13.00 - 13.45 **Industry Sponsored Symposium - see page 321** Pàtria Hall
(Patient advocates not admitted due to local compliance regulations)

13.00 - 13.45 **Advocates session:** Bartók II
"The strength of Patient Experience Data (PED): How advocates can use PED strategically for lasting impact."
Chairs: Nicole Gusset, Yasemin Erbas, Steven Bourke.
(Patient advocates only)

14.00 - 15.45 **Session 5: Optimising treatments for SMA** Pàtria Hall
Chair: Charlotte Sumner, Johns Hopkins University School of Medicine, Baltimore, MD, USA

O23 **Arrested motor axon development drives temporal requirement for SMN restoration in severe SMA**
Keynote Speaker: Charlotte Sumner, Johns Hopkins University School of Medicine, Baltimore, MD, USA

O24 **Rescuing translation defects as a new SMN-independent therapeutic strategy for Spinal Muscular Atrophy**
Ilaria Bruno, Institute of Biophysics, CNR, Trento, Italy

O25 **Respiratory function in adults with Spinal Muscular Atrophy type 1 and 2 treated with risdiplam**
Femke Vercoelen, UMC Utrecht, The Netherlands

O27 **Functional recovery of the neuromuscular synapse in the SMNΔ7 mouse model of spinal muscular atrophy after nusinersen treatment**
Alaó Gatius, Universitat de Lleida/IRBLleida, Spain

O28 **Muscle-specific kinase agonist antibody, ARGX-119, coadministered with an SMN2 splice modulator improves muscle strength and voluntary locomotion in a mouse model of Spinal Muscular Atrophy**
Roeland Vanhauwaert, argenx, Belgium

15.45 - 16.15 **Flash Poster Presentations** — Pàtria Hall

P173 **Beyond spinal motor neurons: cortical projection neuron numerical and morphological alterations reveal selective vulnerability to SMN loss also in the brain**
Roberta Schellino, University of Turin and Neuroscience Institute Cavalieri Ottolenghi, Italy

P88 **Anesthetic risks during intrathecal nusinersen admission in children with Spinal Muscular Atrophy type 1**
Femke Vercoelen, UMC Utrecht, The Netherlands

P44 **Switching DMT in SMA pediatric population: The French experience**
Marta Gomez, Raymond Poincare Hospital, Garches, France

P155 **The natural history of SMA with four SMN2 Copies: Evidence from the Spanish Registry (CUIDAME)**
Karolina Aragon Gawinska Hospital Universitari i Politecnic La Fe, Valencia, Spain

P86 **Management and aspects of pregnancy of SMA on Nusinersen treatment - Case series**
Maria Judit Molnar, Institute of Genomic Medicine and Rare Disorders, Budapest, Hungary

P215 **Prenatal intervention in an SMA Mouse model ameliorates neuro-developmental disorders associated with spinal muscular atrophy**
Charalambos Demetriou, The Dubowitz Neuromuscular Centre, UCL, UK

16.15 - 16.45 **Coffee Break & Poster Session**

16.15 - 17.30 **Poster Session 2** — Gallery Level
Chair: Tom Gillingwater, University of Edinburgh, UK

17.30 - 18.30 **Early Stage Researchers (ESRs) Mentoring Session (by invitation only)** — Bartók II

19.30 - 23.00 **Gala Dinner with Lifetime Achievement Award Ceremony**

SATURDAY 14TH MARCH 2026

08.00 - 09.30

Session 6: New standards of care for SMA — Pàtria Hall

Chair: Andreas Ziegler, Heidelberg University, Germany

O29 Times are still changing - How to screen and whom to treat with how many therapies
Keynote Speaker: Andreas Ziegler, Heidelberg University, Germany

O30 Ensuring best hip management in individuals with SMA across the UK
Giovanni Baranello, Great Ormond Street Institute of Child Health, University College London, UK

O31 Immune and hematopoietic defects in SMA are rescued by SMN repletion
Paula Guillamón, Gil Universitat de Lleida, Spain

O32 Novel SMN1 variants identified by false positive SMA newborn screening test: Therapeutic hurdles and functional solutions
Brunhilde Wirth, Institute of Human Genetics, Univ. Cologne, Germany

O33 Elective preterm birth as a strategy for early intervention in Spinal Muscular Atrophy with two SMN2 copies
Tamara Dangouloff, University Hospital Liege, Belgium

09.30 - 10.00 Coffee Break

10.00 - 11.15

Session 7: Cognitive function in SMA — Pàtria Hall

Chair: Susana Quijano-Roy, Raymond Poincaré University Hospital (UVSQ), Garches, France

O34 Neurodevelopmental phenotype in SMA type 1: Proposal of an evaluation for routine clinical practice
Keynote Speaker: Susana Quijano-Roy, Raymond Poincaré University Hospital (UVSQ), Garches, France

O35 Cognitive development in children with 5q-SMA identified by neonatal screening – 4 years follow-up
Heike Kölbel, Universitätsmedizin Essen, Germany

O36 Cerebellar pathology contributes to motor and cognitive deficits in Spinal Muscular Atrophy
Florian Gerstner, University of Leipzig, Carl-Ludwig-Institute for Physiology, Germany

O37 **SMACK! Project: Impact of the parent-child interaction in the early neurodevelopmental stages of a cohort of children with SMA diagnosed by neonatal screening – A pilot study**
Stefano Parravicini Fondazione, IRCCS Istituto Neurologico Besta, Milan, Italy

11.15 - 12.30 Late Breaking News — Pàtria Hall

O38 **Salnersen - A novel antisense oligonucleotide for Spinal Muscular Atrophy: Phase 1 interim safety and exploratory eficacy results and phase 3 study designs**
Thomas O. Crawford, Johns Hopkins University School of Medicine, Baltimore, MD, USA

O39 **Treating spinal muscular atrophy mice and worms with melatonin leads to improved disease phenotypes**
Melissa Bowerman, Keele University, Staffordshire, UK

O40 **Intrathecal Onasemnogene Abeparvovec (OAV101) for patients with Spinal Muscular Atrophy (SMA): Extended 64-week outcomes from the Phase 3 STEER study**
Crystal M. Proud, Children's Hospital of The King's Daughters, Norfolk, VA, USA

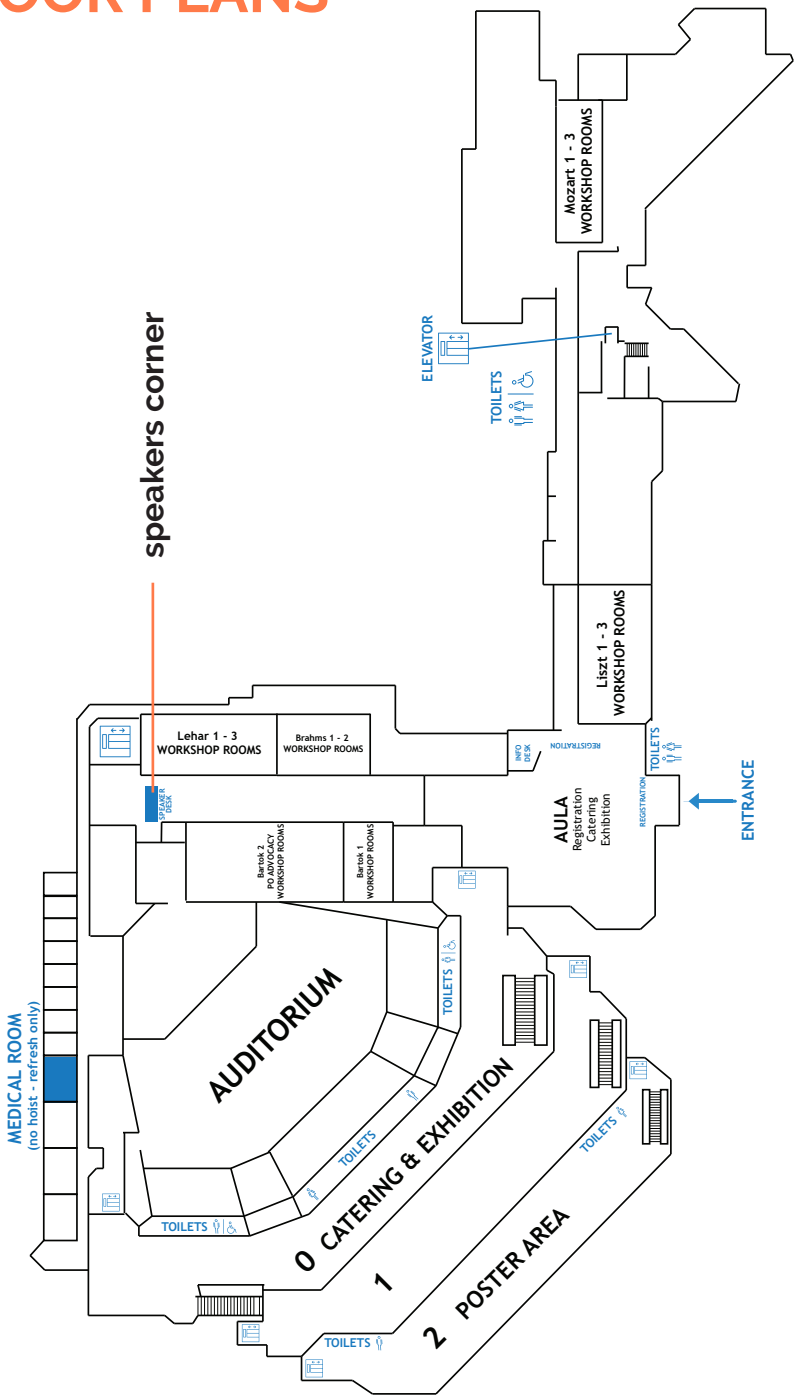
O41 **Prenatal exposure to risdiplam during pregnancy postpones disease onset in a severe SMA mouse model**
Emma R. Sutton, Ottawa Hospital Research Institute, Canada

O42 **Spinal cord stimulation targets circuit dysfunction to improve upper-limb function in non-ambulatory adults with SMA**
Serena Donadio, University of Pittsburgh, PA, USA

12.30 - 13.00 Scientific Poster and Community Awards — Pàtria Hall
Closing Celebrations

13.00 - 13.30 Grab a lunch box in the exhibition area

FLOOR PLANS


NOVOTEL HOTEL
CONGRESS VENUE
speakers corner
ELEVATOR
TOILETS
Mozart 1 - 3
WORKSHOP ROOMS
Liszt 1 - 3
WORKSHOP ROOMS
Lehar 1 - 3
WORKSHOP ROOMS
Brahms 1 - 2
WORKSHOP ROOMS
SPEAKER DESK
INFO DESK
REGISTRATION
TOILETS
ENTRANCE
AULA
Registration
Catering
Exhibition
REGISTRATION
Bartok 2
PO ADVOCACY
WORKSHOP ROOMS
Bartok 1
WORKSHOP ROOMS
AUDITORIUM
TOILETS
MEDICAL ROOM
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TOILETS
TOILETS
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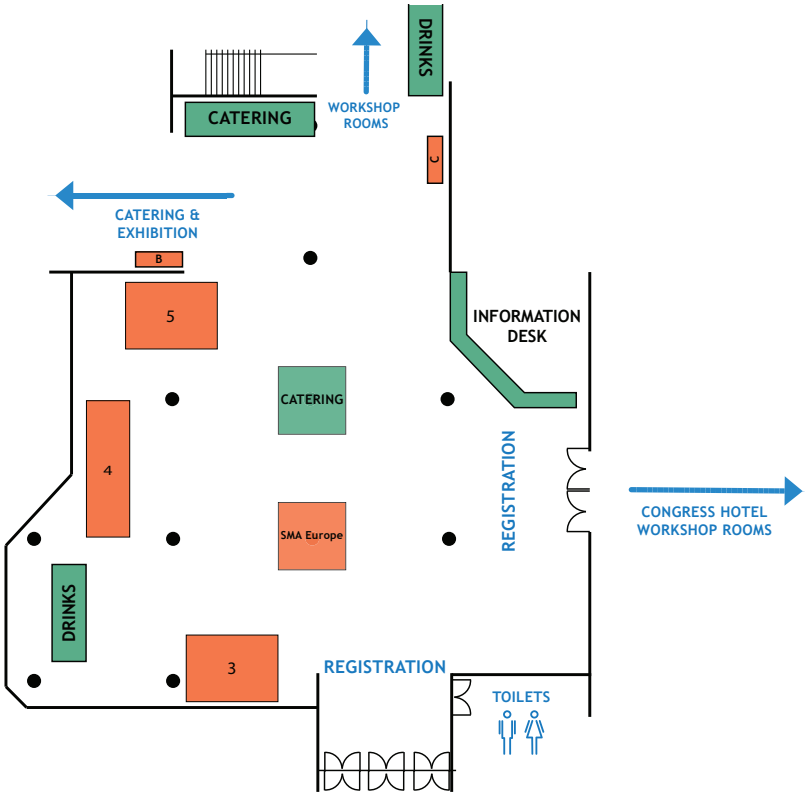
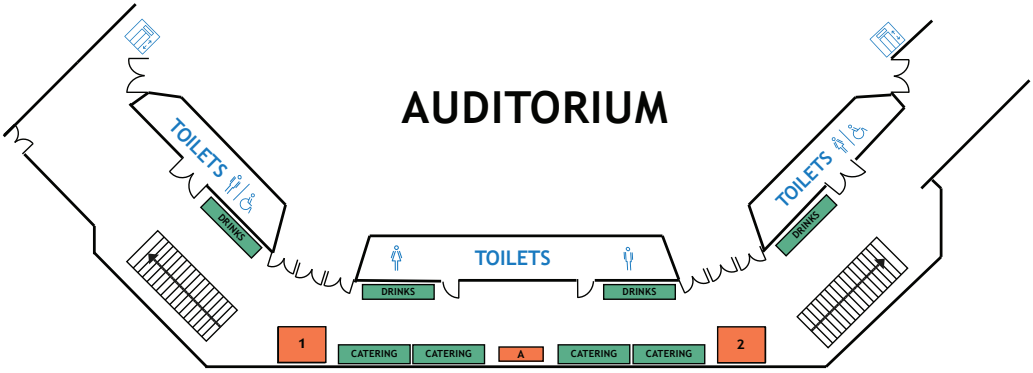
1
2 POSTER AREA
TOILETS
TOILETS

Aula



Mirror corridor



Scientific Committee

Chair. Thomas Gillingwater
Professor of Anatomy at the University of Edinburgh, UK

Vice-Chair. Stefania Corti
Neurologist, Full Professor of Neurology and Principal Investigator of Neural Stem Cell Lab at the University of Milan, Italy

Melissa Bowerman
Professor of Neuromuscular & Skeletal Disorders, School of Medicine, Keele University, UK

Claudio Bruno
Head, Center of Translational and Experimental Myology, IRCCS Istituto Giannina Gaslini, Genova, and Contract Professor in Paediatrics at the School of Medicine, University of Genova, Italy

Peter Claus
Group leader and Professor at the institute of Neuroanatomy and Cell Biology at the Hannover Medical School, Germany

Richard Finkel
Paediatric Neurologist and Director of the Center for Experimental Neuro-therapeutics at St. Jude Children's Research Hospital in Memphis, Tennessee, USA

Ewout Groen
Senior Researcher, SMA Center of Expertise, UMC Utrecht Brain Center, Department of Neurology and Neurosurgery, University Medical Center Utrecht, The Netherlands

Ulrika Kreicberg
Professor of Palliative Care for Children and Young People at the Great Ormond Street Institute of Child Health, University College London, UK

Cécile Martinat
Head of INSERM/UEVE UMR 861 in I-STEM, Paris, France

Christian Simon
Group Leader, Carl Ludwig Institute for Physiology, Leipzig University, Germany

Charlotte Sumner
Professor of Neurology at Johns Hopkins School of Medicine, USA

Ludo van der Pol
Neurologist and Professor of Neurology, Head of the Netherlands SMA center at the University Medical Center Utrecht (UMCU) in The Netherlands

Local Host: Maria Judit Molnar
Professor of Neurology, Psychiatry, Clinical genetics, and Director of Semmelweis University's Institute of Genomic Medicine and Rare Disorders, Budapest, Hungary.

ORAL PRESENTATIONS

O1
Defining and refining biomarkers in Spinal Muscular Atrophy
E. Groen

Dept. of Neurology and Neurosurgery, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht, The Netherlands

Biomarkers are needed to better explain and monitor outcome heterogeneity in spinal muscular atrophy (SMA). Several modalities are in use or under study, including quantitative MRI, EMG (CMAP, CMAP-SCAN) and genetic markers. Here, I will focus on recent developments in molecular biomarkers and their relationship to clinical outcomes. Molecular biomarkers measured in accessible samples, such as blood plasma or serum, may offer objective and sensitive measures of disease activity and treatment response, and help to evaluate and monitor long-term benefit and safety of disease-modifying therapies. Biomarker development in SMA is challenging, as heterogeneous disease severity and treatment outcomes mean that smaller patient cohorts are often underpowered to detect more subtle changes in biomarker candidates or in patient subgroups. In SMA, both CSF- and blood-based neurofilament light (NfL) measurements have been studied most. NfL has potential as a biomarker in in newborn screening cohorts, but its use may be lower in older patients. The numbers of molecular markers linked to treatment response remains limited. I will present two recent efforts to address this knowledge gap. First, we have revisited the concept of a blood-based electrochemiluminescence (ECL) assay to measure SMN protein directly and found that it can be used to reliably quantify SMN in serum at enhanced sensitivity. Moreover, we used translatome profiling of patient-derived fibroblasts to identify functional changes downstream of SMN that improved after in vitro risdiplam treatment. A panel of 12 proteins from this analysis separated genotype and treatment groups and allowed prediction of treatment response in mouse and cellular models of SMA. Finally, I will discuss how these molecular measures align with motor scales and other clinical outcomes, and what adjustments may be needed to improve sensitivity across ages and phenotypes.

O2

Muscle-specific extracellular vesicles: A novel biomarker for Spinal Muscular Atrophy

S. Duguez[1], E. McCallion[2], P. Duc[3], A. Moisan[3], B. L Schneider[4], F. Rage[3], M. Bowerman[2]

[1]Personalised Medicine Centre, School of Medicine, Ulster University, Derry, UK; [2]School of Medicine, Keele University, Staffordshire, UK; [3]IGMM, University of Montpellier, CNRS, Montpellier, France; [4]Bertarelli Platform for Gene Therapy, Swiss Federal Institute of Technology (EPFL), Lausanne, Switzerland

The neuromuscular disease spinal muscular atrophy (SMA) is caused by reduced levels of the SMN protein. There are three approved life-changing and life-saving SMN replacement strategies for SMA. Nevertheless, pre-clinical and clinical studies highlight the need for combinatorial approaches that will include SMN-dependent and -independent treatments. In light of this active and changing SMA therapeutic landscape, there is a pressing need for biomarkers that can inform on severity, disease progression and response to treatment.

Skeletal muscle releases extracellular vesicles (MuVs) that contain lipids, nucleic acids and proteins. Importantly, the number and content of MuVs adapt to and reflect the health status of skeletal muscle. While MuVs have shown biomarker potential in other muscle-wasting conditions, they have yet to be explored in SMA. We therefore set out to explore the potential of MuVs as biomarkers for SMA.
Our analyses of human SMA muscle cells reveals that they exhibit different lipid and protein secretion profiles compared to healthy controls. Similarly, we find significant changes in the MuVs characteristics (number, size, lipid content and protein content) in $Smn^{2B/-}$ SMA mice during disease progression. Importantly, treating $Smn^{2B/-}$ SMA mice with an SMN restoring treatment (scAAV9-*SMN1*) corrects many of these defects. Interestingly, we also observe MuV changes in hypomorphic Smn-depleted mice ($Smn^{2B/+}$, $Smn^{+/-}$ and $Smn^{2B/2B}$), but not to the extent of those observed in the SMA mice themselves.

Overall, our results suggest that MuVs may be a novel and valid biomarkers for SMA disease progression, SMN levels and response to treatment.

O3

Therapeutic and biomolecular effects of long-term Nusinersen treatment in 5q Spinal Muscular Atrophy type 2 and 3: A long-term CSF proteomic study

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5q-associated spinal muscular atrophy (SMA) is a monogenic disease marked by the progressive loss of alpha motor neurons, resulting in muscle atrophy and weakness. Although intrathecal administration of the antisense oligonucleotide nusinersen has been shown to alter disease progression, the molecular mechanisms underlying its therapeutic effects remain poorly understood. Moreover, reliable biomarkers to assess treatment response are currently lacking.

In this longitudinal study, 130 cerebrospinal fluid (CSF) samples were collected over 3.5 years from 24 adult patients diagnosed with SMA type 2 or 3 undergoing nusinersen therapy. To capture proteomic changes associated with treatment, CSF samples were analyzed using mass spectrometry, employing two complementary quantification approaches: label-free quantification (LFQ) and tandem mass tag (TMT) isotopic labeling. These proteomic findings were integrated with cellular and metabolic profiles to provide a comprehensive view of treatment-related changes.
Patients demonstrated a median motor function improvement of 2.2 points on the Hammersmith Functional Motor Scale Expanded (HFMSE) after 10 months, increasing to 2.6 points after 34 months of treatment, although there was a marked interindividual variability. CSF analyses revealed an increased number of macrophages with altered morphology during therapy. Interestingly, levels of albumin quotient (qAlb), glucose, and lactate in the CSF were inversely correlated with clinical improvement, suggesting a potential link between metabolic state and therapeutic outcome.

Proteomic profiling identified 1,674 proteins via TMT- and 441 proteins via LFQ-Proteomics. Fourteen proteins showed cosistent regulation across all patients during nusinersen treatment, qualifying them as potetial monitoring biomarkers. Protein expression patterns under nusinersen treatment indicated a reduced inhibition of pathways involved in nervous system development and axonogenesis. Notably, clinical improvement correlated with the upregulation of the proteins -dystroglycan and beta-1,4-glucuronyltransferase 1, a downregulation of complement components, and a negative association with immunoglobulin- and B cell-related pathways. A decrease in lymphocyte counts further highlighted changes in the neuroimmune environment.

Taken together, this integrative proteomic study enhances our understanding of the molecular effects of nusinersen in adult patients with SMA and identifies potential biomarkers that could aid in monitoring therapeutic response and disease progression.

O4

Motor unit patterns correlate with severity in symptomatic patients with spinal muscular atrophy

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Treatment efficacy of DMTs correlates with disease severity and activity at time of treatment. Clinical motor function scores cannot reflect disease severity are insufficiently sensitive to detect differences over relative short periods of time in the months after treatment failing to predict long(er) term treatment efficacy. We therefore need to develop more sensitive methods to predict and detect motor unit function as a biomarker/surrogate for disease activity and response to treatment.
Electrophysiological techniques, including compound muscle action potential (CMAP) amplitude, CMAP scan, motor unit number estimation (MUNE), and repetitive nerve stimulation (RNS) are used for motor unit (MU) characterization and are promising biomarkers to study the pathophysiology of SMA and to monitor treatment response. We systematically evaluated the different components of the MU using an integrated set of non-invasive electrophysiological techniques, across a broad spectrum of disease severity in symptomatic, treatment-naive adolescents and adults with SMA types 1c-4. More specifically, we assessed the CMAP amplitude, CMAP scan, and RNS, in the median nerve of 104 patients with SMA (aged ≥12 years), before the start of DMT. We compared data to a reference group of 65 healthy controls.
Motor unit patterns were significantly altered in patients with SMA, showing severe MU loss and enlarged MUs due to reinnervation. In patients with SMA median CMAP was 4.5 mV (0.3-14), median MUNE 24 (2-152), absolute mean MU size 0.17 mV (0.06-0.6) with a median percentage MU size of 4 (1-50) relative to CMAP. As expected, primary electrophysiological markers of motor neuron loss, including maximum CMAP, MUNE, D50, and N50 are lower in patients with SMA compared to controls, while markers of reinnervation (e.g., mean MU size, A50, and largest unit) are higher compared to controls. Distinct electrophysiological patterns reflected disease severity, independent of age or disease duration. Patterns were characterized by varying proportions of enlarged MUs relative to MU number, with a markedly reduced MU number and high contribution of enlarged MUs in advanced disease stages. Neuromuscular junction (NMJ) dysfunction (≥10% decrement) was present in 13% of patients, irrespective of SMA severity. Clinical motor function scores correlated with greater MU loss and higher contributions of enlarged MUs.
We identified altered MU patterns and NMJ function in patients with SMA, with distinct patterns across SMA severity independent of age or disease duration. These measures may serve as complementary biomarkers for disease severity in patients with SMA.

O5

Multi-omic biomarkers for personalized Spinal Muscular Atrophy management: A multicenter Italian study

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Spinal Muscular Atrophy (SMA) treatment has been revolutionized by three approved therapies: nusinersen, onasemnogene abeparvovec, and risdiplam. However, reliable biomarkers for predicting treatment response remain urgently needed. This multicenter study aimed to identify multi-omic biomarkers for personalized SMA management. We analyzed biological samples from SMA patients (Types 1-3) and controls across five Italian centers. Comprehensive profiling included CSF/serum proteomics (mass spectrometry), metabolomics (D/L-amino acid enantiomers via chiral HPLC), lipidomics, and epigenomics. Patients were assessed at baseline and after 12 months of treatment. Clinical outcomes were measured using CHOP-INTEND (Type 1) and HFMSE (Types 2-3) scales. We developed patient-derived iPSC-based spinal cord organoids and ***C. elegans*** models for validation. HPLC profiling revealed that the L-glutamine/L-glutamate ratio distinguished SMA subtypes and normalized following nusinersen in Type 1 patients, while elevated D-serine/total serine ratios in severe phenotypes correlated with CHOP-INTEND scores, representing novel biomarkers of disease severity and treatment response. Machine learning identified three molecular clusters predicting treatment response with high accuracy. Patient-derived spinal cord organoids and ***C. elegans*** SMA models recapitulated key disease signatures including motor neuron degeneration, reduced SMN protein expression, axonal dysfunction, and metabolism alterations providing two robust platforms for validating biomarkers and screening therapeutic responses. These biomarkers enable early prediction of treatment response and objective therapeutic monitoring, advancing precision medicine for SMA.

O6

Titin and the muscle-brain Axis in SMA: A promising biomarker for Nusinersen therapy across CSF transcriptome and radiological perspective

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Spinal Muscular Atrophy (SMA) is a neuromuscular disorder caused by insufficient levels of the Survival Motor Neuron (SMN) protein. While historically a pediatric disease, milder adult-onset forms exist. Nusinersen, an antisense oligonucleotide (ASO), restores biologically active SMN by modifying SMN2 pre-mRNA splicing. Recent interest has focused on understanding SMA beyond motor neurons, particularly the role of cerebrospinal fluid (CSF) as a source for diagnostic and prognostic biomarkers. This study investigates the CSF RNA transcriptome in adult SMA Type III patients to identify potential biomarkers and therapeutic targets. We performed RNA-sequencing on CSF samples from three genetically confirmed adult SMA Type III patients. Samples were collected at baseline (T0) and at multiple time points after Nusinersen treatment (T4, T6, T8, T10, T13, and T16 injections). Differentially expressed (DE) cell-free RNAs were identified by comparing each post-treatment time point to the baseline. We also correlated the transcriptomic data with muscular radiological observations (Fat Fraction, Cross-Sectional Area, Intramuscular Fat Fraction) and motor function parameters (Hammersmith Functional Motor Score Expanded and 6-minute walk test). A progressive decrease in the number of DE transcripts was observed over time, with a peak at T4 (115 DE transcripts) and T6 (229 DE transcripts), followed by a plateau.

This molecular trend mirrors the stabilization of the clinical phenotype after an initial improvement. Gene ontology analysis of shared DE transcripts between early (T4) and late (T16) time points revealed a strong enrichment for pathways related to muscle structure and function, including "Striated Muscle Hypertrophy" and "Skeletal Myofibril Assembly." Notably, the muscle structural proteins Titin (TTN) and Nebulin (NEB) were among the most prominent DE genes. Titin levels were maximally upregulated at T4 and progressively decreased with therapy, showing a significant negative correlation with motor function scores. This suggests Titin levels may serve as an effective marker for treatment efficacy. Our findings highlight a systemic, muscular component to SMA pathogenesis beyond the classical motor neuron dysfunction. The CSF RNA signature in adult-onset SMA patients, particularly the downregulation of muscle-related transcripts like Titin, shows a direct correlation with clinical and radiological improvements following Nusinersen therapy. This study identifies Titin and Nebulin as promising auxiliary biomarkers for monitoring treatment efficacy and suggests that future research should explore the functional role of Nusinersen in restoring muscle health in SMA patients.

07
A novel optogenetic cell therapy approach to restore innervation in ALS
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One of the earliest characteristic features of motor neuron diseases (MNDs) such as Amyotrophic Lateral Sclerosis (ALS) is the 'die-back' of motor axon terminals and breakdown of neuromuscular junctions (NMJs). This results in an inexorable progression of muscle weakness, atrophy and paralysis, eventually leading to premature death. We have previously demonstrated a novel strategy to overcome muscle denervation and restore muscle force in a nerve injury model of muscle paralysis that could have therapeutic value for restoring muscle function in MND/ALS patients. This cell replacement strategy uses stem cell-derived motor neurons that have been genetically modified to enable their neural activity to be optically controlled using pulses of light (optogenetics). Following engraftment into peripheral nerves of wild-type mice, these mouse embryonic stem cell-derived motor neurons are capable of functionally reinnervating target muscles following nerve injury. Acute optical stimulation of the engrafted motor neurons induces target muscle contraction and force production in a physiological manner.

We have recently extended these findings to show that this approach leads to robust muscle reinnervation in the highly aggressive SOD1G93A mouse model of ALS. Importantly, reinnervation is maintained until extremely late-stage disease, even when the replacement motor neurons are engrafted after symptom onset. Furthermore, a regimen of daily optical stimulation of the engrafted motor neurons showed significant benefits, including reinforced connectivity between engrafted motor neurons and muscle fibres, enhanced maximal force of the targeted muscle elicited by optical stimulation, and prevention of atrophy of muscle fibres that are reinnervated by engrafted motor neurons.

Our results show for the first time that peripherally engrafted stem cell-derived motor neurons can robustly and reliably reinnervate target muscles, even in a rapidly progressing, aggressive mouse model of ALS. With regular optical stimulation, these replacement motor neurons can enhance muscle function in previously affected, denervated muscles. Together, these advances pave the way for an assistive therapy that could benefit all MND/ALS patients.

O8

Biomimetic viscoelastic hydrogels promote motor neuron outgrowth and modulate astrocyte behavior for Spinal Muscular Atrophy regeneration applications

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Spinal muscular atrophy (SMA) is a severe neurodegenerative disorder caused by loss of motor neurons, leading to progressive muscle weakness and atrophy. While therapies targeting the genetic cause of SMA have improved outcomes for children, effective treatments for adults with SMA remain elusive, partly due to the need to regenerate lost tissue and the challenge of delivering therapeutics directly to the spinal cord to promote motor neuron growth. Biomaterial scaffolds offer a promising solution by enabling localized delivery of drugs and cells while providing a supportive 3D environment for neuronal regeneration. Here, we developed an implantable hydrogel scaffold that mimics the unique biophysical properties of the spinal cord, and through exploiting biophysical interactions promotes healthy and SMA motor neuron growth, modulates astrocyte responses, and delivers growth factors locally for SMA applications.

To inform hydrogel design, we first performed mechanical testing on wild-type and Δ7 SMA mouse spinal cords. Both exhibited highly viscoelastic (the liquid-solid like property of tissues/materials) and fast-relaxing characteristics, with SMA tissue demonstrating increased viscoelasticity and compromised mechanical properties (stress relaxation half-times of ~4s (WT) and ~1s (SMA)). Based on these findings, we engineered synthetic alginate hydrogels with tuneable viscoelasticity (stress relaxation half-times ~1–30s; stiffness <2500 Pa) to replicate these native spinal cord properties. When seeded with iPSC-derived motor neurons from wild-type and SMA patients, fast-relaxing viscoelastic hydrogels significantly enhanced both WT and SMA neurite outgrowth compared to slower-relaxing, elastic or stiffer scaffolds. IPSC astrocytes seeded within these soft, viscoelastic hydrogels displayed enhanced process branching, migration, and adopted favourable stellate morphologies, in contrast to the rounded, hypertrophic morphology seen in stiffer/elastic scaffolds.

A computational model of astrocyte growth, as well as cytokine analysis, confirmed that soft, viscoelastic 3D scaffolds promote astrocyte branching, enhance neurotrophic and angiogenic cytokine release, and reduce secretion of pro-inflammatory cytokines. Bulk RNA sequencing further showed upregulation of neural and metabolic support pathways, suggesting polarization to a neurotrophic phenotype. Soft, viscoelastic hydrogels were then loaded with glial-derived neurotrophic factor (GDNF), a growth factor known to promote neuronal survival. GDNF-loaded scaffolds displayed sustained delivery and when delivered ***in vitro*** through conditioning, significantly enhanced neurite extension in both WT and SMA motor neurons. Moreover, localized delivery of GDNF by these hydrogels to adult mouse spinal cord slice cultures promoted robust process outgrowth, with the combination of optimal scaffold biophysical properties and localized GDNF delivery yielding maximal spinal cord outgrowth.

Overall, we developed a biomimetic hydrogel system that mimics native spinal cord properties, supports SMA motor neuron growth, polarizes astrocytes toward a neurotrophic phenotype, and enables localized growth factor delivery. This platform offers a promising new strategy to facilitate regeneration in SMA and related neurodegenerative conditions.

O9

Neuromuscular organoids reveal developmental transcriptomic dysregulation in SMA

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Spinal muscular atrophy (SMA) is a rare inherited neuromuscular disease characterized by the dysfunction of the thoracic and lumbar neuromuscular system, affecting motor neuron survival, muscle organization and neuromuscular junction stability. Numerous animal models have been developed to recapitulate the neuromuscular defects in SMA. However, due to genetic and physiological differences in the neuromuscular system between humans and other species, animal models developed to date do not adequately recapitulate the human condition. To overcome this limitation, several cellular models based on the differentiation of human induced pluripotent stem cells (hiPSC) have been developed. Recently, a three-dimensional model has been described that captures the developmental processes of the human neuromuscular system.

To investigate the consequences of SMA on human neuromuscular development, we have optimized a differentiation protocol to obtain neuromuscular organoid from both healthy and SMA hiPSC lines. After 50 days of differentiation, SMA organoids exhibited pronounced defects in skeletal muscle organization and increased muscle cell death, whereas neuronal compartments did not display obvious morphological perturbations. To evaluate SMA-associated molecular alterations across the diverse cell populations present in neuromuscular organoids, we performed multi-omic single-nucleus RNA sequencing, integrating 3' gene expression and chromatin accessibility profiles.

Preliminary results and bioinformatic analyses allowed annotation of distinct cellular populations, including neuromesodermal progenitors, neurons, motor neurons, glial cells, myogenic progenitors, skeletal muscle fibers, and fibroblasts. Pseudo-bulk differential expression analysis identified a total of 1,546 dysregulated genes across all populations between control and SMA organoids. Cluster-specific analysis revealed marked deregulation of cytosolic ribosomal subunits and RNA polymerase II components, as well as perturbations in neuronal differentiation programs. In skeletal muscle clusters, we additionally observed alterations in cell–cell and cell–matrix adhesion pathways. Chromatin accessibility analysis is ongoing to further investigate the impact of SMA on gene regulatory landscapes.

Collectively, these findings underscore the potential of neuromuscular organoids as a robust human model to dissect the molecular and cellular mechanisms underlying SMA. This platform provides critical insight into neuromuscular developmental dysregulation and offers a foundation for identifying therapeutic strategies aimed at restoring proper neuromuscular development or enhancing cell survival in SMA.

O10

A novel mouse model of x-linked Spinal Muscular Atrophy offers a platform for preclinical development of UBA1 targeting therapeutics

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X-Linked Spinal Muscular Atrophy (XL-SMA) is a rare, monogenic form of neuromuscular disease which has been unmodelled and untreated in the wake of recent progress in therapy development. In collaboration with The Mary Lyon Centre at MRC Harwell, we have now created and characterised the first mammalian model of XL-SMA: a mouse line which reproduces a patient mutation in the causative gene encoding ubiquitin activating enzyme 1 (UBA1). This novel model exhibits decreased bodyweight due to muscle loss, reduced motor activity, and phenotypic cellular and molecular changes which replicate patient symptoms. As such, the XL-SMA mouse model has enabled us to start investigating the relationship between UBA1 mutations and neuromuscular disease. Furthermore, as we have previously tested an AAV-UBA1 gene replacement therapy in other indications, the mouse model has provided the ideal platform for our pilot-testing of a potential treatment for X-Linked SMA.

O11

Primary cortical neuron cultures as a novel reliable in vitro model to test treatment efficacy for Spinal Muscular Atrophy

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Spinal Muscular Atrophy (SMA) is a neurodegenerative disorder affecting lower motor neurons (MNs) and leading to muscle atrophy, due to mutation of the Survival of Motor Neuron 1 (SMN1) gene, which encodes SMN protein. Experimental studies from our group also demonstrated the impairment of upper MNs and a selective decrease in the number of layer V pyramidal neurons in the motor cortex of SMNΔ7 mice, which recapitulate a severe model of SMA.

Based on this evidence, our study aims to better understand the involvement of upper MNs in the disease pathology and to validate their use for the screening of new compounds for therapy. Indeed, approved therapeutic approaches for SMA might not address the global neurodegenerative process that causes progressive functional decline beyond childhood in less severe SMA types. Moreover, a large number of older patients living with chronic symptoms might not benefit from SMN-inducing treatments. To this purpose, the drug repurposing (DR) strategy appears an interesting approach to provide alternative therapeutic options minimizing the time and cost of drug commercialization.

We cultivated primary cortical neurons from the SMNΔ7 postnatal day 1 mice and found out that under basal conditions, SMA neurons show significantly reduced vitality and altered morphology compared to wild-type (WT) neurons. Specifically, the soma size, neurite length and branching performed by Neurolucida and NeuroExplorer softwares, were impaired in SMA neurons compared to WT. Interestingly, all the parameters were rescued after treatment with known compounds (i.e. Valproic Acid, 4-aminopyridine and N-acetylcysteine), already tested in either preclinical or clinical context for SMA.
We then investigated the efficacy of a novel compound (10H-Phenothiazine) never tested in SMA field, known to exert neuroprotection and to target altered mechanisms in Parkinson's and Alzheimer's disease. Interestingly, compound administration to SMA cortical neurons induced significant neuroprotective effects increasing cell body area, neurite length and branching compared to vehicle-treated SMA cells. Altogether, these findings confirm that cortical neuron cultures represent a reliable in vitro SMA model for drug testing and that 10H-Phenothiazine has a neuroprotective potential both in SMA. Currently, we are also conducting additional studies using a DR approach through high-content screening in a C. elegans SMA model, aiming to identify FDA-approved drugs and validate them in our in vitro models.

O12

Significant microvascular pathology is driven by specific SMN depletion in endothelial cells: The 'EndoSMA' mouse

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Spinal Muscular Atrophy (SMA) is a genetic neuromuscular disorder caused by the loss of the ***SMN1*** gene. This leads to reduced production of the survival motor neuron (SMN) protein. SMA is traditionally considered a motor neuron disease affecting the spinal cord's ventral horn. However, growing evidence supports a broader, multisystemic pathology involving peripheral organs and tissues. Data from both SMA patients and animal models indicate defects in the microvasculature. These defects are likely driven by abnormal intrinsic endothelial phenotypes. Additionally, the presence of blood biomarkers indicative of vascular damage demonstrates an ongoing vascular phenotype in living patients. Importantly, vascular pathology in SMA has the potential to play a key role in disease pathogenesis.

Severe SMA can be modelled by mice null for the ***SMN1*** gene but carrying a single human ***SMN2*** allele. In this study, we developed a novel endothelial-specific SMA mouse model (Endo SMA). In this model, ***SMN1*** is selectively deleted in endothelial cells while carrying a single human ***SMN2*** allele. To explore the contribution of endothelial dysfunction to SMA pathology, we examined the vasculature in the retina and tail as organ models. These mice exhibited postnatal vascular abnormalities, including significant defects in retinal vessel development and persistent vascular abnormalities of the tail.

Whole-mount retinal immunohistochemistry was performed at postnatal day 7 using anti-PECAM1 to label endothelial cells. Vascular networks were quantified using AngioTool software. Assessing parameters such as total vessel length, total vessel area, total number of junctions, and lacunarity. In addition to the vessel outgrowth calculation. Statistical analysis (unpaired t-test, n = 6 per group) revealed significant differences across parameters. Endo SMA retinas showed reduced vessel outgrowth (1713 ± 193.7 µm, Mean±SD) compared with controls (2064 ± 25.95 µm, $p < 0.01$). Lacunarity, an inverse measure of vascular network complexity, was higher in Endo SMA retinas (0.2880±0.02580 Mean±SD) than controls (0.2066±0.01205µm, $p<0.0001$), indicating a less complex vascular bed. These findings confirm that endothelial SMN depletion alone is sufficient to impair vascular development. Ongoing work is investigating whether similar defects occur in other organs.

Our findings provide strong evidence that vascular involvement in SMA is not just a secondary consequence of motor neuron loss. It may be a fundamental aspect of disease pathology. This model offers valuable tools to study the systemic nature of SMA and opens potential avenues for vascular-targeted therapeutic strategies.

O13

Mitochondrial dysfunction in Spinal Muscular Atrophy: Emerging insights from disease mechanisms to therapeutic targets

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Remarkable progress in gene-based therapies for spinal muscular atrophy (SMA) has significantly improved patient lifespan and quality of life. However, these treatments, while compensating for SMN protein deficiency, remain non-curative. Many patients continue to exhibit motor impairments, pointing to unresolved disease mechanisms and novel phenotypes arising from SMN loss in non-neuronal tissues, underscoring the need for complementary therapeutic strategies. Mitochondrial dysfunction is increasingly recognized as a key contributor to SMA pathology. In a muscle-specific SMA mouse model, we previously showed that dysfunctional mitochondria accumulate due to impaired autophagy-lysosomal degradation. These mitochondria exhibit excessive calcium uptake and elevated reactive oxygen species (ROS), leading to respiratory chain defects. Notably, rescuing the myopathic phenotype also restored mitochondrial morphology and gene expression. To investigate whether mitochondrial dysfunction is also a primary feature in human SMA cells, we used patient-derived iPSCs differentiated into motor neurons. Electron microscopy revealed altered mitochondrial cristae and disrupted mitochondria–ER contact sites (MERCs), which are essential for calcium and lipid exchange. To gain deeper insight into the molecular basis of these abnormalities, we performed integrated transcriptomic and metabolomic analyses. This multi-omics approach revealed coordinated dysregulation of pathways involved in energy metabolism, including altered NADH/ redox balance and impaired flux through the TCA and urea cycles. Additional disruptions in calcium signaling, amino acid metabolism, and neurotransmitter pathways were also observed, potentially contributing to excitotoxicity, metabolic stress, and neuronal degeneration. Finally, network analysis identified key microRNAs (miRNAs) as post-transcriptional regulators contributing to the observed structural and metabolic defects. Together, our findings support a mitochondria-centered model of SMA pathogenesis and highlight miRNA-mediated metabolic regulation as a promising complementary therapeutic target.

O14

Adipokines in adult patients with Spinal Muscular Atrophy Type 3: Challenging the canonical narrative

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Spinal muscular atrophy (SMA) is a severe neuromuscular disorder characterized by the degeneration of alpha motor neurons in the spinal cord, leading to progressive proximal muscle weakness and paralysis. Patients with SMA type 3 (juvenile, Kugelberg-Welander disease) initially have the ability to walk unaided, but experience a gradual decline in motor abilities over time. The lifespan is not affected by the presence of the disease, but the studies of metabolic consequences are strikingly missing. Several studies suggest that adiponectin deficiency contributes to the development of insulin resistance, with lower adiponectin levels closely associated with greater insulin resistance and hyperinsulinemia. However, the role of adiponectin in different types of sarcopenia and its connection to insulin sensitivity remains controversial.
The purpose of this study was to evaluate leptin and adiponectin levels in patients with SMA type 3 and explore their association with markers of insulin sensitivity.

This cross-sectional study included 23 adult patients with SMA type 3 (SMA group) and 18 community-based healthy volunteers. Anthropometric parameters, body composition, body fat percentage, surrogate markers of insulin sensitivity (Homeostasis model assessment of insulin resistance index—HOMA-IR and ISI Matsuda), and circulating levels of leptin and adiponectin were measured in all participants.

Insulin resistance was present in 91.3% of patients with SMA type 3, as determined by HOMA-IR and ISI Matsuda insulin sensitivity markers. In the control group, 64.7% had insulin resistance (IR) according to HOMA-IR, while 44.4% met the ISI Matsuda criterion for IR, showing a significant difference in peripheral insulin sensitivity between groups. A significant difference in serum adiponectin levels was observed between patients with SMA type 3 and the control group, whereas there was no significant difference in serum leptin concentrations. Hyperadiponectinemia was observed in 50% of adult patients with SMA type 3. Hyper, but not hypoadiponectinemia could predict detrimental or maladaptive metabolic pathways.

Our results suggest that in this specific type of hereditary neuromuscular disease, the interplay between sarcopenia and insulin leads to adiponectin resistance, challenging the canonical narrative between insulin sensitivity and adiponectin and indicating a need for further research.

O15

Oxidative stress in Spinal Muscular Atrophy (SMA): Cellular mechanisms and antioxidant therapeutic potential

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Oxidative stress is increasingly recognized as a key contributor to neuromuscular disease pathology, driving progressive muscle degeneration, functional decline, and impaired regeneration. Antioxidant therapies have demonstrated benefit in preclinical and clinical contexts. In Duchenne Muscular Dystrophy (DMD), N-acetylcysteine (NAC) reduces reactive oxygen species (ROS)-mediated protein degradation and enhances muscle quality in mdx mice (PMID: 35746858). Similarly, combinatorial antioxidant regimens outperform monotherapies, as illustrated in Facioscapulohumeral Muscular Dystrophy (FSHD). In clinical trial NCT01596803, a daily antioxidant combination (vitamins C, E, zinc, selenium) improved quadriceps strength, muscle volume, and quality of life while lowering oxidative stress markers (PMID: 38574978).

Spinal Muscular Atrophy (SMA), caused by mutations in the SMN gene, is characterized by motor neuron degeneration and progressive atrophy. While the contribution of oxidative stress to SMA pathogenesis remains unclear, evidence suggests increased redox vulnerability. To investigate this, we established SMN-depleted fibroblast models (shSMN) and controls (shScramble). Under chronic oxidative stress (20% O_2 _vs. physiological 3% O_2), SMN-deficient cells displayed pronounced hypersensitivity, partially rescued by antioxidant treatment.

Acute oxidative stress induced by potassium bromate ($KBrO_3$) revealed impaired recruitment of DNA repair proteins to chromatin in SMN-deficient cells, indicating compromised repair capacity. This defect may promote accumulation of oxidative DNA lesions, contributing to cellular vulnerability and neurodegenerative features of SMA.

Collectively, these findings implicate disrupted redox homeostasis and defective DNA repair in SMA pathology. Given the inevitability of endogenous oxidative damage, antioxidant-based strategies may represent a viable therapeutic avenue.

O16

Mitochondrial and redox perturbations in SMA: Insights from multi-organ omics and therapeutic targeting of the NRF2-KEAP1 axis

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Three disease-modifying therapies for spinal muscular atrophy (SMA) are now approved, yet no cure exists, and a substantial number of patients remain partial or non-responders. While SMN expression is ubiquitous, its regulation and tissue-specific consequences remain incompletely understood. Redox biology, although critical for cellular resilience, has been superficially investigated in SMA.

We investigated redox and mitochondrial perturbations using the Taiwanese mouse model. Multi-organ proteomics and biochemical analyses were performed across seven tissues in five experimental groups: wild-type (WT), heterozygous (HET), SMA, and animals injected with SMN-augmenting antisense oligonucleotides (ASOs) in both HET and SMA backgrounds. This comprehensive design allowed us to evaluate both disease- and treatment-specific effects.

Our analyses revealed profound and tissue-specific disruptions of redox enzymes. Mitochondrial-redox perturbations persisted despite ASO treatment in neuronal and muscular organs. In the liver, partial recovery of the NRF2-KEAP1 axis was observed, yet enzymes of the heme biosynthesis pathway remained unrecovered. In contrast, the kidney displayed a unique disruption of endoplasmic reticulum-mitochondria redox crosstalk, a phenomenon not previously reported in SMA. Notably, this study provides the first kidney proteomics dataset in the Taiwanese model, and proteomic analysis demonstrated that this kidney-specific redox-mitochondrial dysfunction was fully rescued by ASO treatment. These findings underscore both the novelty of our dataset and the tissue-specificity of therapeutic responses.

To bridge these findings to human systems, we analysed fibroblasts from SMA type I patients and healthy controls. Pharmacological activation of the NRF2-KEAP1 axis significantly increased proliferation of SMA type I fibroblasts compared to control cell lines already at 48h of incubation. Moreover, pre-incubation with NRF2-targeting analogues before oxidative stress, followed by recovery under treatment, rescued SMA fibroblasts from stress-induced cell death.

Together, these data establish SMA as a systemic redox-metabolic disorder and position the NRF2-KEAP1 cascade as a therapeutic target. A combinatorial approach integrating SMN restoration with redox-directed therapies may improve clinical outcomes, particularly for non-responders to current treatments.

O17

SMN protein levels impact the metabolism of neuroactive amino acids in preclinical models and SMA patients

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SMA is a major genetic cause of infant mortality, resulting from homozygous loss of the SMN1 gene and reduced SMN protein levels. Although recent disease-modifying therapies have significantly improved survival rates and motor function in affected individuals, they do not offer a cure. Many patients continue to experience muscle weakness, metabolic instability, and varied responses to treatment. This situation underscores the need for SMN-independent treatment strategies and reliable biomarkers for personalized disease management.

My seminar summarizes our findings on how SMN deficiency disrupts amino acid metabolism in animal models and SMA patients of varying disease severity before and after Nusinersen treatment.

First, we demonstrate that the key excitatory neurotransmitter, L-glutamate, is significantly reduced in the cerebrospinal fluid (CSF) of untreated SMA1 patients. Notably, Nusinersen restores glutamate levels in these infants, indicating a link between SMN and the balance of neuroactive amino acids. In line with clinical data, we found that D-serine supplementation improved motor symptoms in SMNΔ7 mice.

Second, we observed a deficiency of L-arginine in the spinal cords of SMA mice and in the CSF of untreated SMA1 patients. Similar to L-glutamate, Nusinersen restored L-arginine levels in these infants. Since L-arginine is crucial for nitric oxide signaling, nitrogen metabolism, and energy production, our findings connect the loss of SMN to both synaptic and vascular dysfunction, which have been noted in severely affected infants.

Third, we identified a deficiency of taurine in the brainstem and CSF of untreated SMA1 infants, which was corrected with Nusinersen. Taurine is one of the most abundant inhibitory neurotransmitters in the developing mammalian CNS and possesses antioxidant properties. Thus, our data suggest that taurine supplementation could be a beneficial addition to adjunctive therapy.

Lastly, we found a selective disruption of central dopamine metabolism in SMA1 patients requiring gastrostomy and tracheostomy. These patients had lower levels of the dopamine-related metabolite DOPAC and exhibited negligible improvement on the CHOP-INTEND scale following Nusinersen treatment.
In conclusion, our research indicates that dysregulation of amino acid metabolism is a common characteristic of SMA. By integrating preclinical and clinical evidence, we propose that personalized amino acid supplementation may serve as a viable, SMN-independent therapeutic approach for improving clinical outcomes of current treatments.

O18

Sensory-motor neuronal dysfunction: An essential pathomechanism in animal models and patients of SMA

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SMA is a disease characterized by motor neuron degeneration and muscle atrophy resulting in severe movement deficits. However, dysfunction of sensory synapses is an event prior to neuronal death, raising the possibility that SMA is a disease of motor circuits. Movement is executed through balanced excitation-inhibition in spinal motor circuits, while prolonged imbalance of excitation-inhibition causes dysfunction at both single neuron and circuit levels. We recently reported that dysfunction and loss of proprioceptive excitatory synapses is a key signature both in mouse models and SMA patients. We showed that Type 3 SMA patients exhibit impaired proprioception together with dysfunction of their synapses on motor neurons assessed by the Hoffmann (H) reflex. Postmortem analysis revealed a moderate loss of spinal motor neurons along with reduced excitatory sensory synapses and altered potassium channel expression in motor neurons from Type 1 SMA patients. Importantly, improved motor function and fatigability in Type 3 SMA patients and mouse models treated with SMN-inducing drugs were correlated with expanded function of sensory–motor circuits, captured accurately by the H-reflex.

To investigate whether there any changes in excitation-inhibition could impact motor behavior in SMA, we used functional, morphological, and viral-mediated approaches in SMA mice, and discovered that vulnerable SMA motor circuits fail to respond homeostatically to reduced sensory excitation and instead, increase inhibition. This aberration is mediated mostly by both recurrent and reciprocal inhibitory circuits facilitated by Renshaw cells and Ia inhibitory interneurons respectively. The increase in inhibition in SMA imposed an excessive burden on motor neurons and further restricted their recruitment, since reducing inhibition, either genetically or pharmacologically, improved neuronal function and motor behavior in SMA mice. Thus, the disruption of excitation-inhibition balance is a major maladaptive mechanism downstream of proprioceptive sensory synaptic dysfunction.

The clinical significance of the sensory-motor dysfunction in SMA is highlighted by our recent collaboration with Dr Capogrosso (Univ. Pittsburgh; ClinicalTrials.gov: NCT05430113) where we reported that epidural spinal cord stimulation (SCS) - which can activate proprioceptive fibers subthreshold - improved motor function in three Type 3 SMA patients. In particular, delivery of SCS for ~1 month (2h/day) led to improvements in muscle strength (up to +180%), gait quality (+40%) and endurance (6-MWT: +26 m), and paralleled an increase in motor neuron firing rates. These results were perfectly aligned with observations from our previous reports in SMA mice. This evidence highlights the prominence of sensory dysfunction in controlling motor neuron function in SMA pathogenesis and propose SCS as a powerful and novel therapy that can be used in combination with any of the currently three approved SMA therapies.

O19

Cortical GABAergic dysregulation and metabolic alterations in a Spinal Muscular Atrophy mouse model

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Although Spinal Muscular Atrophy (SMA) is primarily considered a lower motor neuron (MN) disease caused by SMN deficiency, emerging evidence highlights the motor cortex (CRTX) as a critical site of pathology, with morphofunctional alterations and maladaptive plasticity. Given limited access to patient samples, preclinical models are essential to clarify motor cortical involvement and underlying mechanisms in SMA pathogenesis. Building on our previous observation of upper MN vulnerability in SMA mice, we dissected cortical inhibitory GABAergic signalling, metabolism, and interneuron (IN) function in the sensorimotor (SM) CRTX and in primary neuron-astrocyte co-cultures from a severe SMA mouse model, compared to WT controls. Bioinformatic and biochemical analyses revealed stage-specific alterations in GABAergic pathways and metabolite profiles, particularly at late stage (P12), indicating a critical window of cortical network vulnerability. Imaging and molecular studies showed: (i) GABA neuron loss (-38%); (ii) impaired GABA synthesis (GAD65/67); (iii) parvalbumin IN deficits (-30%) with reduced GABAergic synapses in layers II/III and V (-28%, -38%). Electrophysiology confirmed decreased inhibitory input onto layer V pyramidal neurons. Further analyses showed that SMN loss, as pre-mRNA splicing factor, impairs the neuron–astrocyte GABA/glutamate/glutamine cycle by altering astrocytic transporter expression (SNAT5: -45.11%; GAT3: +29%), reducing neuronal glutamine supply and affecting astrocytic GABA reuptake. These changes cause neuronal GABA deficiency and suggest astrocytic GABA accumulation, leading to cortical GABAergic dysfunction that contributes to SMA pathology and highlights SMN's role in neurotransmitter regulation. Our data support a mechanistic model in which SMN deficiency impairs cortical GABAergic networks, expanding our understanding of cortical mechanisms in SMA and providing a framework for cortical-targeted therapeutic strategies.

O20

Advancing assessment of perceived physical fatigability using the SMA EFFORT

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Disease-modifying therapies (DMTs) altered the natural history of SMA, but fatigability remains an unmet need. Although DMTs have shown variable efficacy in attenuating fatigability on performance-based clinical assessments, their real-world impact remains unknown. Attempts to measure the impact of fatigability are complicated by a lack of SMA-specific tools that can effectively measure experienced fatigability. The SMA EFFORT is a patient-reported outcome measure that anchors physical activity to intensity and duration and quantifies perceived physical fatigability (PPF) across SMA function.

Characterize PPF in teens and adults with SMA.

Participants (≥12 years; N=121) completed the SMA EFFORT and self-reported clinical characteristics. PPF was rated using a 5-point Likert scale with pertinent activities (N=30) performed in the past 30 days. Total and four subscale scores were generated, with higher scores representing more PPF. Perceived energy in the past 30 days was assessed with a single item for comparison. Statistical tests examined differences in PPF by current function and treatment, and regression examined unadjusted and adjusted associations of PPF with treatment.

Among respondents (N=121), 27.3% were non-Sitters, 46.3% Sitters, and 26.4% Walkers, with mean age of 36.7 years (range: 12-78). Most participants were female (55.4%), and 84.3% (N=102) reported treatment with either risdiplam or nusinersen only. Scoliosis surgery and respiratory support were reported in 44.6% and 35.5% of participants, respectively.

Walkers endorsed more activities (21.0±2.7), followed by Sitters (16.0±3.2), and non-Sitters (11.1±3.6), $p<.0001$. Non-Sitters reported greater PPF than Sitters and Walkers, $p<.0001$. Walkers reported greater PPF on the Mobility subscale, $p=.0007$, while non-Sitters reported more PPF in the ADL and Postural Control subscales, $p=.0004$, $p<.0001$, respectively. No PPF differences on the Exercise/Recreation subscale were observed. Participants on risdiplam were weaker, $p=.0498$, had greater use of respiratory support, $p=.009$, and reported more PPF than those on nusinersen, $p=.048$. Adjusting for these factors revealed no difference in PPF between treatment groups, $p>.05$. Weak associations of PPF with energy, $=-.0676$, $p<.0001$, and age, $=.0031$, $p=.0004$, were found.

Despite DMTs fatigability persists in individuals with SMA. The SMA EFFORT provides a standardized, individualized PPF assessment that can evaluate treatment effects. In this study, fatigability was present across the phenotypic spectrum and did not differ between treatment groups when adjusting for impairment severity, suggesting similar therapeutic benefit. As ancillary therapies with distinct biological targets become available, this tool facilitates a symptom-specific method to assess efficacy. Ongoing work will evaluate the scale's sensitivity to change and explore its application to younger children.

O21

smn-1 regulates motoneurons and dopaminergic neurons crosstalk in C. elegans

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Recently SMA has been re-defined as a multi-system disorder affecting also different neuronal cells other than motor neurons. This includes autonomic nervous system, sensory and proprioceptive neurons, cholinergic interneurons and astrocytes and is in line with the fact that the causative gene, Smn1, is a ubiquitous gene with housekeeping functions. For this reason, modeling the disease with a small and simple animal model like C. elegans is useful to elucidate the effect of genetic variations on other neurons beside motor neurons. In iPSCs-derived motor neurons from SMA patients, in mice and in C. elegans smn-1 null mutants, the dopaminergic pathway resulted to be highly dysregulated at the transcriptional and post-transcriptional level. Taking advantage of multiple C. elegans SMA models mutated in smn-1, the C. elegans ortholog of Smn1, we investigated the connection between SMA and dopamine (DA) in vivo. Interestingly, through HPLC in total extracts we found a reduction in DA and serotonin content in C. elegans SMA models. The reduction in DA level was also confirmed in vivo in whole animal, by detecting DA in dopaminergic neurons by formaldehyde induced fluorescence.

Moreover, we demonstrated that mutations in smn-1 lead to dopaminergic neuronal disfunction, by quantifying the DA-related capacity of C. elegans to sense food, with a cell-autonomous role of smn-1 specifically in this neuronal cell type. To further dissect the involvement of the DA pathway we used both a pharmacological and a genetic approach. We demonstrated that the administration of the L-DOPA, the DA precursor, was sufficient to partially rescue DA intracellular reduction and the behavioral defect. Moreover, we obtained a similar effect overexpressing bas-1, the orthologue of dopamine-decarboxylase, in the dopaminergic neurons.

Therefore, we investigated the involvement of the DA pathway in SMA related neurodegenerative phenotypes. To do so, we overexpressed bas-1 in DA neurons and we observed a rescue of SMA-related MNs degeneration and the locomotion impairment, as well as a worsening of MNs degeneration when cat-2, the ortholog of the tyrosine hydroxylase, was silenced. Our data are in line with two recent papers showing alterations in monoamine metabolism and a loss of catecholaminergic synapses in SMNΔ7, further stressing the predictive validity of our model. Taken together our results point out to a dysfunction of the dopaminergic system in SMA that may account for some alterations observed in some SMA patients. Moreover, we also demonstrated, for the first time, that the modulation of the DA pathway can ameliorate neurodegenerative phenotypes suggesting a crosstalk between DA and MNs in SMA.

O22

Motor neuron pathology drives spinal circuit defects and phenotype of spinal muscular atrophy with respiratory distress type 1

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Spinal Muscular Atrophy with Respiratory Distress Type 1 (SMARD1) is a rare neuromuscular disorder caused by mutations in the IGHMBP2 gene, leading to respiratory failure, distal muscle atrophy, and early lethality. The neuromuscular degeneration (NMD) mouse model replicates key pathological features of SMARD1, including motor neuron loss, muscle denervation, and a distally progressing phenotype. However, the impact on spinal motor circuits and the cellular mechanisms underlying disease progression remain largely unknown. To address this, we employed confocal microscopy, whole-cell patch-clamp recordings, a novel inter-sectional viral/genetic approach, and motor behavior assessments to investigate spinal motor circuit dysfunction in the NMD mouse model. Our findings reveal that muscle denervation precedes motor neuron degeneration and is followed by a selective loss of spinal excitatory synapses in distal motor circuits. Notably, this synaptic vulnerability in NMD mice closely parallels observations in spinal cord tissue from a SMARD1 patient. As motor symptoms develop, proprioceptive dysfunction also emerges, characterized by Ia synapse loss, delayed and reduced synaptic neurotransmission. Remarkably, genetic restoration of IGHMBP2 in motor neurons fully rescued sensory-motor circuit integrity, prevented muscle atrophy, and restored motor function in NMD mice, demonstrating that motor neurons are the primary drivers of SMARD1 pathology. These findings provide critical mechanistic insights into motor neuron-driven proprioceptive dysfunction and support motor neuron-centered therapeutic strategies as a promising approach for treating this currently incurable disease.

O23

Arrested motor axon development drives temporal requirement for SMN restoration in severe SMA

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While current disease modifying therapeutics (DMTs) improve outcomes particularly when delivered neonatally, significant disability often persists in severe SMA patients. We have previously shown in severe SMA mice and type I human autopsy tissues that many SMA motor axons fail to grow in radial diameter and do not undergo radial sorting by Schwann cells beginning prenatally. We have now demonstrated these pathologies in two autopsy cases of SMA type 0, although the developmental arrest is more pervasive and associated with widespread active axon degeneration. In severe SMA cases treated post-symptomatically with DMTs, motor axon degenerative pathologies are attenuated but developmental impairments persist. Treatment of severe SMA mice in utero with either transplacental risdiplam or amniotic fluid delivered splice switching ASO can improve but does not completely reverse developmental defects. In SMAΔ7 mice lacking Sarm1, a primary executor of axons, axon degeneration is transiently halted postnatally. Surviving axons remain diminutive and un-ensheathed by Schwann cell cytoplasm further confirming their developmental arrest. To further understand the molecular drivers of this developmental arrest, we are performing single nucleus RNA sequencing (snRNAseq) of SMA and control motor neurons (MNs) isolated from severe SMA mice, expressing GFP-tagged Sun1, a nuclear envelope protein, in choline acetyltransfersase (ChAT) positive neurons, at different fetal ages. Preliminary data at E17.5 demonstrate more significant gene expression changes in medial motor column (MMC) MNs compared to lateral column (LMC) and phrenic motor column (PMC) MNs. Gene ontology analysis identified pathways involved in neuron development and differentiation as well as regulation of cell communication and signaling.

O24

Rescuing translation defects as a new SMN-independent therapeutic strategy for Spinal Muscular Atrophy

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In addition to its role in ribonucleoparticle biogenesis, the Survival Motor Neuron (SMN) protein, deficiency of which causes Spinal Muscular Atrophy (SMA), has been proposed to act as a ribosome-associated protein. SMN-primed ribosomes supervise the translation of a specific subset of mRNAs that are enriched for enhancer regulatory sequences in the 5' UTR and rare codons at the beginning of the coding sequence. In SMA, decreased levels of SMN protein lead to an impairment in protein synthesis that can be rescued with the administration of antisense oligonucleotides that restore SMN expression. Although three SMN-enhancing therapies are available, SMA remains incurable, underscoring the urgency for complementary and SMN-independent strategies.

Here, we explored novel SMN-independent and translation-based approaches to complement existing therapies. Exploiting a cellular model of SMA and a dual luciferase sensor of SMN-specific translation, we performed an automated screening and identified four small molecules that rescue SMN-specific translation defects.

After validation, one molecule emerged as the most promising candidate, exerting the strongest restorative effect on translation. We showed that the treatment with this compound rescued defects in ribosome association with mRNAs, and that this effect is independent of SMN. Using Limited Proteolysis-Coupled Mass Spectrometry, we revealed a novel and translation-related target that exhibits strong binding affinity for the compound in molecular docking assessments.

Strikingly, in vivo analyses in three C. elegans models of SMA demonstrated that all four compounds mitigate neurodegeneration and improve motor performance, with the most promising candidate additionally extending survival. The same compound also rescues motor axonal defects in a SMA zebrafish model.

Our study identified a promising compound that restores SMN-specific translation defects, pointing to novel SMN-independent therapeutic strategies. These findings ultimately support the development of complementary treatments with the potential to improve patient care and quality of life in SMA.

O25

Respiratory function in adults with Spinal Muscular Atrophy type 1 and 2 treated with risdiplam

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Spinal Muscular Atrophy (SMA) causes progressive respiratory muscle weakness, resulting in recurrent respiratory tract infections, scoliosis, and chest wall deformities, all of which contribute to progressively declining lung function. Respiratory problems are a major cause of morbidity and mortality in the severe types of SMA. Risdiplam, an oral *SMN2*-splicing modifier, has been shown to improve motor function in patients up to 26 years and ventilation-free survival in infants with SMA. Little is known about effects on respiratory function in adults with SMA. This study aims to evaluate the effect of risdiplam on respiratory muscle strength and lung function in adults with SMA.

We conducted a nationwide cohort study in treatment naïve adults with SMA type 1 and 2 who received risdiplam as part of the compassionate use program. Prospective data on respiratory muscle strength were collected every eight months during a 40-month follow-up. Data on lung function were also collected, although not at standardized time points. The primary outcome was the change in respiratory muscle strength at fixed time points during follow-up compared to baseline. The secondary outcome was the effect of risdiplam on forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and peak expiratory flow (PEF), assessed by comparing the annual rate of decline in lung function before and after starting risdiplam.

We included 72 adult patients with SMA type 1c (n= 10) and type 2 (n= 62). We observed an improvement in maximal expiratory pressure (MEP) after 24 months (Δ +4.1 cmH_2O, p=0.006), 32 months (Δ +5.8 cmH_2O, p=0.004), and 40 months (Δ +5.1 cmH_2O, p<0.001) of treatment. In addition, our results showed an improvement in maximal inspiratory pressure (MIP) after 8 months (Δ +5.5 cmH_2O, p=0.001), 16 months (Δ +5.6 cmH_2O, p=0.008), 24 months (Δ +6.2 cmH_2O, p=0.008), 32 months (Δ +7.6 cmH_2O, p<0.001), and 40 months (Δ +5.4 cmH_2O, p=0.029) of risdiplam. We did not observe a change in slope of FVC after starting risdiplam. FEV_1 and PEF improved after starting risdiplam with mean differences in slopes of 2.0% (p=0.012) and 3.4% (p<0.001) respectively. At treatment initiation, 36 patients required ventilatory support (n=28 non-invasive ventilation, n=8 invasive ventilation), none were able to discontinue ventilation. During follow-up, 7 patients started non-invasive ventilation, while 2 patients required a tracheostomy.

This is the largest study to date evaluating the effect of risdiplam on respiratory muscle strength and lung function in adults with SMA. Our study demonstrates that both inspiratory- and expiratory muscle strength improved in adults after starting risdiplam. We did not observe a change in FVC. FVC reflects not only respiratory muscle strength, but is also affected by other factors such as scoliosis, chest wall stiffness and atelectasis, which are often already advanced in adults with SMA.

O27

Functional recovery of the neuromuscular synapse in the SMNΔ7 mouse model of spinal muscular atrophy after nusinersen treatment

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Spinal muscular atrophy (SMA) is caused by insufficient levels of survival motor neuron (SMN) protein, leading to profound neuromuscular defects, including severe dysfunction of the neuromuscular junction (NMJ). Nusinersen, an antisense oligonucleotide that restores SMN expression, has markedly improved the clinical outcome of SMA patients, although its ability to fully halt disease progression remains limited. The extent to which neuromuscular connectivity can be restored, and the long-term efficacy of the treatment, are unclear. Here, we investigated the impact of nusinersen on NMJ morphology and function in the SMNΔ7 mouse model of severe SMA at two different stages.

Newborn SMNΔ7 mice received a single intracerebroventricular (ICV) injection of nusinersen (6.5 mg/kg) or saline. Body weight, motor function, and survival were monitored. Neuromuscular transmission was examined in the transversus abdominis muscle –a muscle severely affected in SMA– at postnatal day (P) 14 (end-stage in untreated mice), and at P30 (median survival of treated mice) by performing ex vivo electrical nerve stimulation and intracellular recordings of postsynaptic potentials. NMJ and myofiber morphology were analyzed by immunohistochemistry and confocal imaging.

Nusinersen treatment at P0-1 increased body weight, improved motor performance and doubled median survival of SMNΔ7 mice. Electrophysiological recordings revealed that SMN restoration largely prevented SMA-related neuromuscular defects, with a preservation of quantal content at both P14 and P30. Nevertheless, evoked endplate potential (EPP) and miniature EPP (mEPP) amplitudes remained elevated, likely reflecting the persistence of a smaller myofiber size. Moreover, EPP rise time was slightly prolonged in P14 nusinersen-treated SMA mice compared to age-matched controls, consistent with a modest delay in postsynaptic receptor maturation, as suggested by our preliminary morphological examination of NMJs. Preliminary analyses of spontaneous and asynchronous neurotransmitter release in nusinersen-treated SMA mice showed similar patterns to controls at both P14 and P30, suggesting normalized presynaptic Ca^{2+} handling.

In summary, early ICV administration of nusinersen substantially rescued neuromuscular connectivity in SMNΔ7 mice, with no overt decline at end stages. These findings are consistent with the prominent, though partial, improvement in motor behavior and the fact that disease progression is only partly dependent on neuromuscular defects. Prenatal interventions and/or combinatorial approaches need to be considered to achieve more complete preservation of neuromuscular and organic functions in SMA patients.

O28

Muscle-specific kinase agonist antibody, ARGX-119, coadministered with an *SMN2* splice modulator improves muscle strength and voluntary locomotion in a mouse model of spinal muscular atrophy

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The severity of spinal muscular atrophy (SMA) is influenced by the survival motor neuron (***SMN)2*** gene**.** SMN-C3, a small molecule splicing modifier that enhances exon 7 inclusion in the ***SMN2*** gene, has demonstrated benefits in SMA D7 mice. Muscle function often remains impaired in patients with SMA despite standard SMN upregulating therapies. ARGX-119, a muscle-specific kinase agonist, has been shown to improve muscle function in mouse models of neuromuscular diseases. This study evaluated the coadministration of ARGX-119 with SMN-C3 in a mouse model of SMA. D7 mice treated with ARGX-119 and a high dose of SMN-C3 and D7 mice treated with vehicle and a high dose of SMN-C3 were included. SMN-C3 was administered at 3 mg/kg daily on postnatal days (PND) 1–20 (intraperitoneal injection [IP]) and 9 mg/kg daily on PND 21–49 (oral gavage). ARGX-119 (10 mg/kg) or vehicle (IP) was administered on PND 1, 21, and 42. Voluntary locomotor function was measured in a BlackBox chamber on PND 21 and 48 after dosing. As the masseter muscle is vulnerable in D7 mice, ***in vivo*** function (force measured after electrical stimulation) was assessed on PND 49; mice were then euthanized, and tissues were collected.

Up to 15 mice were included in each group. At PND 21, compared with vehicle-treated mice, mice treated with ARGX-119 showed a statistically significant increase in time spent with both front paws up, along with increases in lower front/hind luminance ratio and hind paw angle. There was no statistically significant difference in distance traveled. At PND 48, the significant difference in lower front/hind luminance ratio persisted. ***In vivo*** maximal force of the masseter muscle did not differ significantly between groups after 7 weeks of treatment. When normalized to body weight, the difference remained nonsignificant. However, when normalized to muscle weight, mice treated with ARGX-119 exhibited statistically significant greater maximal force than those treated with vehicle. At the time of tissue collection, gastrocnemius muscle weight was significantly higher in mice treated with ARGX-119 compared with vehicle-treated mice; there were no statistically significant differences in body weight or the weights of the masseter and tibialis anterior muscles. Coadministration of ARGX-119 and high-dose SMN-C3 led to improvements in muscle function and size, as well as locomotor activities, compared with the administration of SMN-C3 alone in SMA D7 mice. Notably, muscle function alone may be as important as size, as evidenced by the masseter muscle achieving increases in muscle function without a corresponding increase in weight. Data from this proof-of-concept study suggest that ARGX-119 may improve muscle function in patients with SMA and mitigate associated atrophy, warranting clinical development.

O29

Times are still changing - How to screen and whom to treat with how many therapies

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Disease-modifying treatments (DMTs) for spinal muscular atrophy (SMA) have now been available outside of clinical trials for almost a decade. This unique therapeutic success story has fundamentally altered the natural history of the disease: children with SMA now survive and, in cases in which treatment is initiated at the asymptomatic stage, may even achieve age-appropriate motor development.

The implementation of newborn screening for SMA in many countries worldwide, together with strong collaboration within the SMA community, represents another major achievement of recent years. Nevertheless, numerous open questions remain. New treatments continue to enter the market, and interest in combination approaches involving multiple DMTs is increasing.

This presentation aims to provide an objective overview of the current state of scientific knowledge and to stimulate reflection on the next decade of this exceptional success story in spinal muscular atrophy.

O30

Ensuring best hip management in individuals with SMA across the UK

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The 2018 international care recommendations for spinal muscular atrophy (SMA) were published prior to the availability of disease-modifying treatments (DMTs), which have significantly altered the clinical course, phenotype and prognosis of SMA. These guidelines, intended as a global minimum standard of care, were largely focused on paediatric populations and did not account for the novel and evolving phenotypes, now observed as a result of treatment advances.

SMA Care UK is a collaborative initiative involving healthcare professionals, people living with SMA and other stakeholders. Its goal is to update evidence-based standards of care and harmonise best practice in response to the priorities of the SMA community and the changing landscape of SMA.

While the 2018 international standards of care provided a foundation for musculoskeletal management in SMA, hip management was not a primary focus. Individuals with SMA, particularly non-ambulatory patients, are at high risk of hip instability, subluxation and dislocation, driven by muscle weakness, immobility, contractures and scoliosis. Hip displacement can cause pain, seating difficulties and reduced quality of life. In the era of DMTs, which extend survival and broaden phenotypes, hip management remains essential and requires individualised conservative and surgical approaches. These factors underscore the need for clinical guidance to support systematic assessment, monitoring and management of hip health across the paediatric-to-adult spectrum.
In response, individuals living with SMA, expert adult and paediatric healthcare professionals, including Neurologists, Orthopaedic Surgeons, Neuromuscular Physiotherapists and an Orthotist, have undertaken a comprehensive review of the current evidence and practice for hip management in SMA. Drawing on emerging data, evolving clinical experience and identified areas of unmet need, the group will develop guidance covering assessment, monitoring and therapeutic interventions. The group is working with relevant professional bodies and NICE, so that guidance can be endorsed and published once consensus is achieved.

In parallel, gaps in evidence are being highlighted and strategies will be developed to address these, including future evidence-gathering and collaboration with international networks to ensure that updated guidance remains aligned with global best practice.

O31

Immune and hematopoietic defects in SMA are rescued by SMN repletion

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Spinal muscular atrophy (SMA) has traditionally been viewed as a motor neuron disease, but increasing evidence highlights its multisystemic nature. Here, we investigated lymphoid organ alterations in a severe SMA mouse model (SMNΔ7) and in autopsy material from SMA fetuses, newborns and infants with one or two SMN2 copies, predicted to develop type I disease.

In SMNΔ7 mice, immunohistochemistry and flow cytometry revealed marked structural and cellular abnormalities in the thymus, spleen, and bone marrow. These included thymic cortical atrophy, disrupted splenic architecture with mislocalized T and B cells, and impaired B-cell maturation in the bone marrow, suggesting defective hematopoiesis as a key driver of peripheral immune dysregulation. Inflammatory features were also evident, such as elevated interleukin-6 levels and expansion of splenic macrophages. Importantly, early treatment with a nusinersen-like antisense oligonucleotide (SMN-ASO), delivered intracerebroventricularly or subcutaneously, not only improved survival and motor function but also prevented lymphoid tissue abnormalities.

In type I SMA patients, the spleen exhibited architectural disruption and altered immune cell distribution similar to that observed in mice, whereas the thymus appeared largely preserved across developmental stages. These interspecies differences likely reflect distinct patterns of immune maturation and disease progression.

Together, our findings demonstrate that SMN deficiency compromises lymphoid organ development through defective bone marrow function and immune cell maturation. Moreover, early SMN restoration mitigates these defects. This work highlights the immune system as both a contributor to SMA pathology and a potential therapeutic target.

O32

Novel SMN1 variants identified by false positive SMA newborn screening test: Therapeutic hurdles and functional solutions

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Newborn screening (NBS) for spinal muscular atrophy (SMA) enables early diagnosis and treatment of infants with biallelic ***SMN1*** deletions. PCR-based assays identify ~95% of cases via absence of ***SMN1*** exon 7; remaining cases involve rare variants undetectable by standard NBS. We report two newborns (Germany, Australia) identified by NBS as lacking both ***SMN1*** genes. Instead, confirmatory testing identified one ***SMN1*** copy in both, with no ***SMN2*** (P1) or one ***SMN2*** (P2). Sanger sequencing of gene specific long-range genomic amplicons revealed two different 4-bp deletions in ***SMN1*** exon 7 (c.855_858delAGAA in P1 and c.861_864delAAGG in P2), both overlapping the reverse primer site — explaining the false NBS result. Interestingly, both variants caused the same frameshift (p.Arg288Alafs*5), assumed to be potentially harmful. Functional studies demonstrated preserved ***SMN1*** exon 7 splicing and very low SMN protein levels in proband cell lines but comparable thermostability to wild-type SMN. ***In vivo***, both variants fully rescued the early phenotype of established SMA zebrafish model — contrasting with known pathogenic variants.
Population data (gnomAD, carrier frequencies) suggest ~800 individuals of European origin may carry these variants in trans with ***SMN1*** deletions, yet neither has been reported in SMA patients. Moreover, our calculation for newborns in EU27, show that about 2 children are expected to be identified with this particular compound heterozygous genotype: ***SMN1***del/VUS. Additional rare missense variants in the primer or probe-binding regions reported in GnomAD v4.1 and NBS programs may lead to even more false positive or uncertain ***SMN1*** NBS results. Both children remain asymptomatic at 23 months without therapy, avoiding treatment costs of €1.2 million for P1 and AU$2.2 million for P2. These data suggest that low protein level of a novel SMN protein can efficiently mitigate SMA, challenging the assumption that a minimum of full-length wildtype SMN is required for survival, and that comprehensive functional and population-data evidence can decisively influence treatment decisions following NBS. Lastly, to increase diagnostic accuracy, we recommend that any abnormal SMA NBS result that cannot be confirmed by MLPA or dPCR should always be followed up with complete ***SMN1*** sequencing.

O33

Elective preterm birth as a strategy for early intervention in Spinal Muscular Atrophy with two *SMN2* copies

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Timely initiation of therapy has dramatically changed the prognosis of spinal muscular atrophy (SMA), but prenatal diagnosis still raises unresolved questions when the foetus carries only two *SMN2* copies. Evidence suggests neurodegeneration begins during the third trimester, and recent reports of *in utero* therapy illustrate both the potential and the uncertainties of that approach. Here we describe an alternative strategy: planned late-preterm delivery to allow very early postnatal treatment.
The child was identified during pregnancy after her older sibling, with the same genotype, developed motor impairment despite treatment initiated at 18 days of age. Genetic testing confirmed homozygous *SMN1* deletion with two *SMN2* copies. After extensive discussions involving gynaecologists, neonatologists, and paediatric neurologists, a caesarean section was performed at 35 weeks and 4 days. The infant required non-invasive ventilation from birth until day 3 of life, which was attributed to late prematurity. She was discharged on day 17 after achieving feeding autonomy and thermal regulation. Oral risdiplam was initiated on day 2 (D2) of life after MLPA confirmation of the diagnosis. Intravenous onasemnogene abeparvovec was administered at day 59 (D59).

Neurofilament concentrations were normal at birth and stable under risdiplam, with a temporary increase occurring when the oral therapy was stopped just before gene therapy. This pattern suggests that prolonged bridging therapy could potentially help to better control neuronal injury during the transition. Motor development was normal at birth; hypotonia emerged around two months but resolved progressively, with normalization of tone and motor milestones by five months. Follow-up at 7 months remained positive, with the infant continuing to achieve expected motor milestones. Clinical and biological follow-up is ongoing.

This case illustrates that planned preterm birth, coupled with immediate postnatal initiation of therapy, may provide a pragmatic compromise between the ethical and logistical challenges of in utero treatment and the risks of delaying intervention until after term delivery. Prospective data and additional cases are needed to assess whether this approach can reliably prevent early neurodegeneration and improve long-term outcomes in high-risk SMA infants.

O34

Neurodevelopmental phenotype in newborn-detected SMA and early-onset SMA with two SMN2 copies: Proposal of an evaluation adapted to routine clinical practice

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To characterise the neurodevelopmental phenotype in children with spinal muscular atrophy (SMA) type 1 or type 2 with two SMN2 copies, including presymptomatic SMA detected by newborn screening, and to propose a pragmatic evaluation model adapted to routine clinical practice.

Methods: We conducted a cross-sectional, two-centre observational study at Vall d'Hebron Hospital (Spain) and Raymond Poincaré Hospital (France). Nineteen children aged 2–10 years with genetically confirmed SMA were evaluated through a battery of parent-report and clinician-administered tools, including the Child Development Inventory (CDI), Modified Checklist for Autism in Toddlers-Revised (M-CHAT-R/F), Social Communication Questionnaire (SCQ), Child Behaviour Checklist (CBCL), Raven's Coloured Progressive Matrices (CPM), and the Clinical Global Impression–Severity (CGI-S). Associations between developmental delays and clinical modifiers were explored with correlation and regression analyses. Results: Autonomy, fine-motor skills, and expressive language were the most affected CDI domains, with developmental delays widening with age. Numerical cognition remained relatively preserved. Hierarchical clustering identified four phenotypic patterns influenced by age, SMN2 copy number, and timing of treatment initiation. More than half of children screened positive for autism risk, although confounding by motor/bulbar deficits is likely. CBCL scores were largely within normative ranges. CGI-S correlated strongly with receptive/expressive language and social skills. Raven's CPM was feasible in a minority. Conclusion: Children with SMA treated with disease-modifying therapies show heterogeneous but frequent neurodevelopmental impairments, particularly in autonomy, fine-motor and expressive language skills, while numerical cognition is relatively spared. Routine neurodevelopmental surveillance using pragmatic tools such as CDI and CGI-S is warranted, alongside autism screening and early-targeted interventions.

What this paper adds

- A simple screening toolbox (CDI + ASD screening questionnaire + CGI-S) can be applied for detection and quantification of neurodevelopmental problems in SMA.
- Expressive language is the most impaired non-motor neurodevelopmental domain in patients with SMA type I while numerical cognition is relatively preserved.
- Neurodevelopmental problems are variable and different types of involvement and severity exists related with SMA severity, SMN2 copy number and treatment delay.
- The high autism-screen positivity highlights the need for SMA-adapted ASD assessment.

O35

Cognitive development in children with 5q-SMA identified by neonatal screening – 4 years follow-up

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The impaired cognitive development of children with 5q-SMA and two ***SMN2*** copies, despite early initiation of therapy, which was detected during neonatal screening, underlines the crucial role of the SMN protein in the early stages of brain development. Long-term data on the cognitive development of these children are lacking to further elucidate the situation.

A total of 46 families with 47 children identified in newborn screening were invited to have their children tested with the WIPPSY-IV and the CBCL after the age of four.

Twenty-two children with a mean age of 58.15 months (SD = 7.45) were included, 12 girls and 9 boys, 12 patients with two, 5 patients with three, and 5 patients with 4 ***SMN2*** copies. The total IQ score on the WPPSI-IV was in the average range (M = 87.53; SD = 15.96). The non-verbal index (M = 80.42; SD = 20.51), the general ability index (M = 79.13; SD = 20.71), and the cognitive performance index (M = 77.86; SD = 22.08) were all below average. The mean scores for the WPPSI-IV subtest areas of language comprehension (M = 83.35; SD = 16.67) and processing speed (M = 83.64; SD = 15.19) were below average. The mean scores for the subtest areas of visual-spatial processing (M = 94.45; SD = 23.21), fluid reasoning (M = 89.91; SD = 19.42) and working memory (M = 89.09; SD = 23.63) subtest areas were average. All CBCL scales were rated as average by the parents.
In the regression analysis, the Bayley Cognitive Scale scores from our initial study were significantly associated with current IQ scores using the WPPSI-IV (= 0.80, p = 0.002, R^2 = 0.64) and with nonverbal IQ scores (= 0.83, p = 0.006, R^2 = 0.68).

Long-term observation seems to confirm impaired cognitive development in children with SMA and two SMN2 copies. However, a larger group is needed to investigate this more in detail. Functional studies on biomaterials from these children are necessary to better understand the pathophysiological background.

O36

Cerebellar pathology contributes to motor and cognitive deficits in spinal muscular atrophy

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Spinal muscular atrophy (SMA) is a motor neuron disease caused by SMN deficiency, resulting in muscle weakness and impaired movement due to the degeneration of spinal motor circuits. Recent clinical findings suggest that yet to be identified neuronal circuits in the brain contribute to motor and newly emerging deficits in SMA patients. Here, we discover conserved mechanisms of cerebellar circuit pathology associated with progressive Purkinje cell (PC) degeneration selectively in a severe mouse model and Type I SMA patients. Cerebellar pathology is further aggravated by synaptic loss and dysfunction of parallel fibers onto PCs, resulting into reduced functional output of the cerebellar cortex. These impairments arise intrinsically within the cerebellum, independent of established spinal motor circuit pathologies, and contribute to motor deficits in SMA mice. This was further proven via Cre-dependent knockdowns of Smn in PCs, where animals exhibited at old ages, severe and progressive PC degeneration. This resulted in severe motoric impairment in these animals. The PC loss found in the SMA mice on the other hand resulted in early development cognitive impairment, which presented itself with severe reduction in ultrasonic vocalizations, which was partially rescued by PC-selective restoration of SMN. Importantly, treatment with different, clinically-relevant SMN inducing therapies including splicing modifiers and gene replacement demonstrate both overlapping and distinct effects on cerebellar pathology in SMA mice. Together, these findings highlight dysfunction of cerebellar circuits and death of PCs as critical yet underappreciated contributors to motor deficits, which should be considered in care of SMA patients receiving current treatments and for development of future therapeutics.

O37

SMACK! Project: Impact of the parent-child interaction in the early neurodevelopmental stages of a cohort of children with SMA diagnosed by neonatal screening – A pilot study

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Spinal muscular atrophy (SMA) is a rare autosomal recessive neuromuscular disorder, mainly caused by homozygous deletion of the SMN1 gene, leading to progressive motor neuron degeneration. The recent advent of disease-modifying therapies (nusinersen, risdiplam, onasemnogene abeparvovec) has radically changed the disease trajectory. In parallel, the widespread adoption of neonatal screening has enabled early diagnosis, including pre-symptomatic stages, allowing prompt therapeutic interventions. These advances raise new questions regarding the role of early parent-child interactions and the impact of diagnosis-related medicalization on neurodevelopment. Literature is scarce on the influence of caregiver-child relational dynamics in SMA, despite their potential relevance for clinical outcomes and family well-being

This pilot study aimed to investigate early parent-infant interactions in children with SMA diagnosed via neonatal screening, compared with typically developing peers. We focused on interactional patterns across the first year of life, assessing the influence of maternal sensitivity, infant socio-emotional regulation, communicative development, and socio-cognitive responses. A further objective was to explore the psychological impact of diagnostic communication and subsequent medicalization on parental experience and dyadic exchanges.

The study enrolled SMA infants and matched controls, with assessments at ~8, 10, and 12 months. At 8 months, maternal sensitivity and infant socio-emotional regulation were analyzed through remote, free-play sessions, complemented by standardized questionnaires (BDI, STAI, PSI-SF, IBQ-R, SP-2). At 10 months, early communicative behaviors (gestures, vocalizations) were systematically coded during dyadic exchanges. At 12 months, socio-cognitive abilities were examined in a semi-structured interaction including exposure to social and non-social auditory stimuli, allowing evaluation of joint attention, social referencing, and caregiver adaptive responses. Parental perspectives on diagnosis communication were collected through questionnaires and interviews.

Preliminary findings suggest distinctive features of early parent-infant interactions in SMA, with potential modulation by maternal affective states and stress. Data indicate that the experience of diagnosis and medicalization can shape family dynamics and relational patterns, even in pre-symptomatic children who develop comparably to healthy peers.

In the era of neonatal screening and early therapeutic intervention, understanding the nuances of parent-child interaction is essential to optimizing care in SMA. This study highlights the need to integrate psychosocial and relational dimensions into clinical practice, aiming to support both neurodevelopmental outcomes and family well-being.

LATE BREAKING NEWS

O38

Salanersen, a novel antisense Oligonucleotide for Spinal Muscular Atrophy: Phase 1 interim safety and exploratory efficacy results and Phase 3 study designs

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Salanersen (BIIB115) is an investigational, intrathecally administered antisense oligonucleotide (ASO) in development for spinal muscular atrophy (SMA). Salanersen modifies splicing of the SMN2 gene by binding the ISS-N1 region, a region also targeted by nusinersen. However, salanersen has a novel modification to the ASO backbone that leads to high potency, supporting the rationale for dosing only once per year. This Phase 1 study (NCT05575011/EU CT 2023-505643-39) is evaluating the safety, tolerability, pharmacokinetics, and exploratory efficacy of salanersen (40 mg or 80 mg doses) in paediatric participants (aged 0.5–12 years) with SMA who were previously treated with onasemnogene abeparvovec (OA) and have suboptimal clinical status. Exploratory efficacy assessments include neurofilament levels, World Health Organization (WHO) motor milestones, and motor function scales. A previous interim analysis was performed once the older participants in the 40 mg dose cohort (n=8) had completed at least 1 year of follow-up. Salanersen was generally well tolerated at the 40 mg and 80 mg dose levels. In participants with elevated baseline plasma neurofilament levels, salanersen treatment was associated with a 70% reduction by Day 180, which was sustained over time. Of the 8 participants with 1-year follow-up available, 4 (50%) achieved new WHO motor milestones beyond what would be expected based on baseline functional status and time on previous treatment, and clinically meaningful improvements were observed on Hammersmith Functional Motor Scale – Expanded (mean +3.3-point improvement) and Revised Upper Limb Module (mean +5.3-point improvement). This presentation will share new interim results now that all participants have reached 1 year of follow-up. Updated safety and efficacy data will be presented.

Phase 3 studies are being initiated to evaluate the efficacy and safety of salanersen (80 mg dosed once per year) across different SMA populations. Two linked STELLAR studies will assess the efficacy and safety of salanersen in infants diagnosed with SMA who initiate treatment while presymptomatic. STELLAR-1 is an open-label, single-arm study evaluating salanersen in treatment-naive, presymptomatic infants (aged ≤6 weeks) with SMA and 2 or 3 SMN2 copies. STELLAR-2 is a randomized, double-blind, sham-controlled study evaluating salanersen in infants with SMA and 2 SMN2 copies who received treatment with OA at ≤6 weeks of age. An additional SOLAR study will evaluate the efficacy and safety of salanersen in teens and adults. SOLAR is an open-label study that will enrol participants aged 15-60 years who are either treatment-naïve or are transitioning from risdiplam. Study designs will be shared.

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Treating spinal muscular atrophy mice and worms with melatonin leads to improved disease phenotypes

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Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular condition that is increasingly recognized as a multi-systemic disorder in which metabolic dysfunction plays a central role. Reframing SMA pathology from a neurocentric to a metabolic perspective reveals abnormalities in metabolic tissues such as skeletal muscle, liver, pancreas and adipose tissue, including insulin resistance, hepatic steatosis, dyslipidemia and circadian disruption. Although currently approved disease-modifying therapies significantly improve survival and motor function, they do not adequately address peripheral and metabolic pathologies, underscoring the need for the development of complementary strategies aimed at modulating metabolic homeostasis.

We used our previously published work aimed at combining bioinformatics and drug repositioning strategies to identify melatonin as having strong translational potential. The natural hormone melatonin regulates sleep, circadian rhythms and muscle health. Importantly, we and others have described several circadian and sleep perturbations in SMA patients.

We therefore assessed the therapeutic potential and activity of melatonin in SMA Smn2B/- mouse and C. elegans models. We observed that melatonin treatment significantly improved various behavioural, molecular and/or histological pathological phenotypes in SMA mice and worms such as survival, weight, motor function, muscle size and spinal cord health. Interestingly, systemically delivered melatonin showed activity in several tissues, impacting molecular effectors involved in circadian rhythm, glucose metabolism, mitochondria biogenesis and browning of white adipose tissue. Together, these findings position metabolism at the forefront of targets for SMA treatments and provide strong rationale for exploring metabolism-targeted second-generation therapies such as melatonin to complement currently approved disease-modifying treatments.

O40

Intrathecal Onasemnogene Abeparvovec (OAV101) for patients with Spinal Muscular Atrophy (SMA): Extended 64-week outcomes from the Phase 3 STEER study

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STEER was a phase 3, multicenter, randomized, sham-controlled, double-blind study evaluating the efficacy and safety of single-dose intrathecal (IT) OAV101 in treatment-naive, sitting and never-ambulatory patients with SMA aged 2 to <18 years. The primary objective—comparing OAV101 IT vs sham in change from baseline in HFMSE through Week 52—was met, with OAV101 IT demonstrating a statistically significant, clinically meaningful increase in HFMSE compared with sham. Eligible patients completing the 52-week comparative phase entered a second part with 3 additional months of follow-up.

Patients were randomized to OAV101 IT or sham and followed through Week 52. From Week 52 + 1 day to Week 64, sham-treated patients switched to OAV101 IT, and those initially treated with OAV101 IT received sham. This analysis reports efficacy outcomes for patients who received OAV101 IT in the first part, with HFMSE and RULM changes from baseline evaluated through Week 64. Cumulative safety was assessed for all patients who received OAV101 IT.

A total of 126 patients received study treatment (n=75 OAV101 IT; n=51 sham) during the first part of the study. Of the 75 OAV101 IT-treated patients, 67 continued into the second part; 46 of 51 sham patients entered the second part and received OAV101 IT. During the combined follow-up period of 15-months post-treatment, mean HFMSE scores continued to increase, demonstrating sustained and progressive motor function gains without other SMN-targeted therapy. Least-squares mean (LSM) HFMSE changes from baseline were 2.41 (95% CI: 1.54–3.27) at Week 52 and 2.75 (95% CI: 1.61–3.88) at Week 64. LSM change from baseline in RULM increased from 2.47 (95% CI: 1.72–3.21) at Week 52 to 2.93 (95% CI: 2.04–3.81) at Week 64). The most common AEs among all OAV101 IT–treated patients (n=121) were upper respiratory tract infection (28.1%), pyrexia (19.8%), and vomiting (18.2%). AEs of special interest included hepatotoxicity (8.3%), transient thrombocytopenia (7.4%), and signs/symptoms that may be suggestive of dorsal root ganglia toxicity (2.5%). Transaminase elevations were generally mild and transient, with no Hy's law cases.

Patients receiving OAV101 IT in STEER showed continued motor improvement through Week 64. The cumulative safety profile of OAV101 IT through Week 64 was consistent with the comparative phase of the study, with no new safety signals identified.

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Prenatal exposure to risdiplam during pregnancy postpones disease onset in a severe SMA mouse model

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Disease modifying therapies (DMT) have transformed the therapeutic landscape for Spinal Muscular Atrophy (SMA). Significant evidence from clinical trials and real-world data indicate early treatment is beneficial for therapeutic outcome in patients with SMA. While promising, early post-natal treatment with any of the approved DMTs fall short of a cure. Importantly severe (type 0) patients with SMA present with prenatal disease onset including cardiac anomalies and reduced foetal movements. It is during this prenatal window that developing motor neurons have the greatest need for SMN. Risdiplam is a small molecule SMN2 splicing modifier that is orally delivered, administration to a pregnant mother could offer a noninvasive therapeutic strategy to target foetal disease. Recently, a report described administration of risdiplam to one human foetus with SMA demonstrating an apparent ameliorating effect on the disorder.

However, there is an absence of comprehensive preclinical data to validate this approach. We have investigated this novel therapeutic strategy in the SMND7 severe mouse model by administering a high dose of RG7916 ((risdiplam (10mg/kg/day) to a pregnant dam during gestation (E9.5-19.5). We demonstrate an increased risk of abortion following high dose treatment. Gestation length was not significantly impacted by treatment, with no malformed pups at birth. Whole brain size remained proportional to body weight, no overt anatomical brain pathology was seen in SMA pups. SMA pup weight and motor function were fully restored and comparable to healthy controls, treatment also resulted in an earlier onset of postnatal weight gain in SMA mice compared to healthy controls. High-dose RG7916 (delivered E9.5-19.5) significantly increased survival. Early embryonic exposure to SMN rescued motor neuron number, muscle atrophy and neurofilament accumulation at the neuromuscular junction at postnatal (p) day 13. Some empty neuronal beds were present at P13 indicative of motor neuron loss, likely resulting from termination of treatment at birth. Postnatal SMN protein levels do not remain elevated at P13 following embryo-exposure only to RG7916. Our research suggests that targeting SMN therapy to the embryo can postpone disease onset, yet sustained benefit likely depends on a combined prenatal and postnatal therapeutic strategy. Overall, by restricting risdiplam exposure to the embryo and terminating treatment at birth, we have been able to isolate and assess therapeutic effects attributable solely to embryo exposure.

O42

Spinal cord stimulation targets circuit dysfunction to improve upper-limb function in non-ambulatory adults with SMA

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Pre-clinical models indicate that a hallmark feature of SMA is not only MN death but also MN dysfunction due to decreased proprioceptive inputs, leading to hyperexcitable MNs with prolonged refractory periods and paradoxically reduced firing rate. As such, along with available therapies that prevent MN death, targeting spinal sensorimotor circuitry to improve circuit and consequently MN function is necessary to treat motor deficits that persist despite SMN restoration. Since spinal cord stimulation (SCS) activates sensory afferents, we hypothesized that increased input to MNs via SCS could address this circuit dysfunction. Indeed, we previously showed in three ambulatory adults with SMA that SCS improves strength, gait quality, and endurance in only 4 weeks. Here we report a follow-up trial (STUDY21080158) building on our prior work which tested cervical SCS in three non-ambulatory adults with SMA in the absence of exercise to explore improvement of function of the upper limb. We temporarily implanted (29 days) epidural leads over the cervical spinal cord of three non-ambulatory participants (SMA04: male, 56 y/o baseline RULM: 8/37, SMA05: female, 21 y/o, baseline RULM: 20/37, SMA06: male, 60 y/o, baseline RULM: 34/37). To isolate stimulation effects from exercise, SCS was delivered unilaterally, using the contralateral arm as an internal control. Participants received 2 hours/day of stimulation during strength testing and 3D reaching tasks. Despite differences in age and disease severity, all participants showed increased strength (grip: up to +184%, elbow ext: up to +190%) and improved reaching kinematics, including increased smoothness, range of motion, and movement velocity. Gains were consistently higher in the stimulated arm, indicating that exercise alone is unlikely to explain the improvements. Importantly, over the four-week study period, participants also reported meaningful functional gains in daily life, including being able to unbutton a shirt, independently open doors and open the car's gas tank door. Together, these results suggest that cervical SCS can complement SMN-based therapies by targeting spinal circuit dysfunction to improve upper-limb motor function in SMA.

POSTER SESSION 1

THURSDAY 12TH MARCH 2026

16.15 - 17.30

P1

Comprehensive proteomic analysis of the matrisome identifies extracellular matrix dysregulation in SMA muscle cells

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Spinal muscular atrophy (SMA) has traditionally been regarded as a motor neuron disease. However, growing evidence indicates that skeletal muscle plays a primary role in disease progression and symptom manifestation. Our group has recently reported intrinsic defects in myofiber development, cytoskeletal organization, and regenerative capacity even in the absence of overt motor neuron loss (Berciano et al., 2024).
In skeletal muscle, the extracellular matrix (ECM) is essential for myogenesis, myofiber maturation, and repair. This highly organized three-dimensional network, comprising collagens, glycoproteins, proteoglycans, and secreted regulators collectively known as the matrisome, ensures communication between muscle fibers, satellite cells, motoneurons, and capillaries. Alterations in ECM composition and organization are increasingly recognized as key contributors to muscle dysfunction and fibrosis in both primary matrix disorders and neuromuscular diseases.
Although we are now in the "therapeutic era" of SMA, joint contractures remain among the most disabling clinical manifestations and cannot be fully explained by denervation or muscle weakness. We therefore hypothesize that changes in ECM composition and organization within skeletal muscle and/or tendon tissue contribute to structural abnormalities, compromising the mechanical properties of the myotendinous unit and favouring contracture development despite current treatments.

Primary muscle-derived cell cultures (myoblasts, myotubes, and myofibroblasts) were obtained from SMNΔ7 and wild-type (WT) mice at postnatal day (P) 2. Protein fractions corresponding to intracellular lysates, secreted proteins, and extracellular vesicles were analyzed by LC–MS/MS. Raw data were processed, and differential expression analyses were performed. The resulting data were then subjected to functional enrichment analysis using KEGG and Gene Ontology databases. Target genes were further validated by performing qRT-PCR using whole-muscle and tendon RNA samples from WT and SMNΔ7 mice at P12.

Proteomic profiling of SMNΔ7 muscle-derived cells revealed extensive alterations in metabolic and structural pathways, particularly those related to oxidative phosphorylation, mitochondrial organization, protein translation, and amino acid metabolism, consistent with impaired bioenergetic capacity and proteostasis. Processes involving actin cytoskeleton organization, vesicle-mediated transport, and stress response were also disrupted in SMNΔ7 muscle cells, indicating defective cellular homeostasis.
Notably, more than 100 ECM-associated proteins were differentially expressed in SMNΔ7 cells. Upregulated proteins included collagens, matricellular components, and ECM remodelling enzymes, highlighting profound matrisome alterations in SMA muscle.

Our comprehensive proteomic analysis of skeletal muscle-derived cells has revealed widespread dysregulation of the SMA muscle matrisome and suggest that ECM dysregulation may contribute to myopathic and contracture phenotypes in SMA. These findings provide new insights into SMA pathogenesis and identify potential therapeutic targets beyond motor neuron restoration.

P3

Intensive speech-language rehabilitation in a child with SMA Type 1: Case report

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Spinal Muscular Atrophy (SMA) type 1 is a rare and severe neuromuscular disorder characterized by progressive degeneration of motor neurons, with repercussions on vital functions such as breathing, swallowing, and communication. Children with SMA type 1 are at high risk of dysphagia, feeding difficulties, and speech limitations, although cognitive and comprehension aspects are preserved. Speech-language intervention is essential to ensure clinical safety, stimulate oral functions, and support alternative communication strategies. This study aims to report the clinical experience of patient M.M.L.C., who underwent intensive speech-language rehabilitation provided by a supervised intradisciplinary team, highlighting strategies and observed outcomes.

Patient M.M.L.C. underwent an intensive protocol with two daily speech-language therapy sessions, five days per week, conducted by three speech-language pathologists with complementary areas of expertise: dysphagia, orofacial myofunctional therapy (feeding-focused), and orofacial myofunctional therapy for language with support of Augmentative and Alternative Communication (AAC). Supervised by an SMA specialist speech-language pathologist, improvements were observed in tolerance to oral feeding, acceptance of intraoral stimuli, and expansion of oral motor repertoire including speech. Significant communicative progress was also achieved through AAC resources, facilitating interaction with family and healthcare team. Specialized supervision was crucial to standardize approaches, integrate therapists, and ensure clinical safety, resulting in positive overall evolution.

The case of M.M.L.C. demonstrates that intensive speech-language rehabilitation, structured with distinct therapeutic focuses and supervised by an SMA specialist, enhances functional gains in feeding and communication. The division of approaches and the use of AAC proved effective strategies to improve functionality, reinforcing the relevance of supervised intradisciplinary models in the clinical management of SMA type 1.

P5

Evolution of swallowing in a child with SMA Type I after gene therapy and speech-Language rehabilitation

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Spinal Muscular Atrophy (SMA) type I is a rare and progressive genetic disease characterized by severe hypotonia, loss of motor functions, and oropharyngeal dysphagia. The advent of gene therapy with Onasemnogene Abeparvovec (Zolgensma®) has significantly modified the prognosis of these patients. This study presents the clinical evolution of a child with SMA type I who underwent gene therapy and intensive speech-language pathology follow-up, with a focus on swallowing functionality. Clinical and instrumental assessments were performed at different stages of intervention, using the FOIS scale and videofluoroscopic swallowing study.

Before gene therapy, the patient presented with severe oropharyngeal dysphagia, requiring gastrostomy and showing an increased risk of bronchoaspiration. Videofluoroscopy indicated absence of effective oral ejection, pharyngeal stasis, and silent aspiration. After Zolgensma® administration and continued speech-language rehabilitation three times per week, progressive improvement was observed in oral motor control, more consistent presence of the swallowing reflex, reduced microaspiration, and improved pharyngeal transit. The child's functional classification evolved to moderate/severe oropharyngeal dysphagia, with greater safety for controlled oral feeding at home.

The combination of gene therapy and systematic speech-language intervention demonstrated a positive impact on the functional evolution of swallowing in a patient with SMA type I, highlighting the importance of early and continuous interdisciplinary care to enhance functionality and quality of life.

P7

SMA and feeding selectivity: Impact of speech-language intervention - Case report

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Spinal Muscular Atrophy (SMA) is a neuromuscular disorder characterized by degeneration of motor neurons, with significant motor and bulbar repercussions such as dysphagia and feeding selectivity. Children with SMA type 1 often require early alternative feeding routes for nutritional maintenance. Lack of oral stimulation and structured speech-language follow-up may lead to oral hypersensitivity and food aversion. This study reports the case of a child with SMA type 1, who underwent early gastrostomy and developed severe feeding selectivity due to hypersensitivity, later showing significant improvement after intensive speech-language therapy. The case highlights the importance of early oral sensory-motor stimulation to promote feeding functionality and prevent complications resulting from oral deprivation.

Patient L.O.S.R., male, SMA type 1 with two SMN2 copies, underwent gastrostomy in early infancy without initial speech-language follow-up. He started therapy around one year of age and, until approximately two and a half years, presented significant aversion to intraoral stimuli, marked feeding selectivity, and episodes of dysautonomia during food introduction attempts. With continued structured therapy including oral desensitization, sensory-motor stimulation, and gradual exposure to oral feeding, progressive reduction of aversion and functional improvement were observed. Currently, the patient tolerates intraoral stimuli, demonstrates greater acceptance of new foods, and shows overall progress in feeding experiences.

This case demonstrates that feeding selectivity due to oral hypersensitivity in children with SMA can be reversed with systematic and intensive speech-language therapy, even after late initiation. The positive evolution of L.O.S.R. reinforces the importance of maintaining oral stimulation from diagnosis and of early multidisciplinary intervention to prevent aversions, expand food repertoire, and ensure nutritional safety and quality.

P9

Clinical outcomes of TheraBite treatment in patients living with Spinal Muscular Atrophy type 2 & 3

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Spinal Muscular Atrophy (SMA) Types 2 & 3 frequently cause reduced active maximal mouth opening (AMMO) through progressive weakness and contracture of the mastication muscles. This restriction impacts nutritional intake, oral hygiene, dental care delivery and emergency airway management during medical procedures. There are no existing evidence-based therapies for the treatment of AMMO.

To evaluate clinical outcomes and patient experience of a 6-month Therabite treatment programme.

Patients were selected for treatment from a physiotherapist-led tertiary neuromuscular outpatient clinic (July 2024 – 2025) using predetermined criteria: AMMO < 35mm, overbite <10mm allowing teeth-palate contact, and an ability to manipulate the device independently or with assistance.
The Therabite was calibrated for comfortable stretch without overextension. Treatment compromised three daily treatment sessions of five 30-second sustained stretches. Primary outcomes measured AMMO, active mandibular lateral excursion, and protraction (mm). Patient-reported outcomes included the Jaw Functional Limitation Scale-8 and a custom 10-item yes-no questionnaire. Follow-up assessments at one, three, and six months tracked progress and guided device adjustments.

Of 48 patients with reduced AMMO attending clinic, 39 met eligibility criteria and 15 consented to treatment. Ten had SMA 2 and five had SMA 3 (age range 18-65 years, 10 female). Twelve patients completed the programme. Three withdrew in total due to, insufficient therapy time (n=1), disclosure of a benign tumour proximal to the jaw (n=1), and discomfort from upper incisor overjet (n=1). One patient developed temporal headaches that resolved following programme modification.
All completing patients achieved between a 1 and 8mm increase in AMMO, representing 5-42% percentage improvement. Patient-reported benefits included improved oral hygiene access (n=9), reduced mealtime duration (n=1), increased bite capacity (n=3), improved secretion control (n=1), and reduced gastrostomy dependence through improved oral intake (n=1).

Our findings indicate that Therabite treatment improves AMMO and functional outcomes in selected patients with SMA. Careful patient selection and close monitoring are essential to understand and prevent any adverse effects. Further research should evaluate optimal treatment intensity, comparative device efficacy, and the role of preventative treatment programmes.

P11

An attempt at integration of SMA assessment: Exploring clinical and electro-physiological perspectives

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The advent of disease-modifying therapies (DMTs) has transformed the clinical course of spinal muscular atrophy (SMA), highlighting the limits of traditional outcome measures. Standard motor scales confirm treatment efficacy but do not capture more subtle motor qualitative changes, fluctuations in energy, tremor or fasciculations, or subjective improvements in autonomy and daily functioning reported by patients and caregivers.

This work does not aim to provide definitive answers but to explore whether additional tools may complement current scales and better reflect patient trajectories. We asked: (i) do discrepancies exist between standardized scales and what patients/caregivers perceive? (ii) can relatively simple tools such as AI-assisted video analysis or surface ECG provide additional markers of therapeutic response?

We retrospectively studied 11 SMA patients (7 type 3, 4 type 2; 7 males, 4 females, median age 14.5y). Each contributed three ECG recordings (first, intermediate, last), with repeated measures of fasciculation number (Nf) and amplitude (Af). Linear mixed models with random intercepts were used to test changes across timepoints, with ANOVA for overall effects and pairwise contrasts, adjusting for SMA type, sex, age, and SMN2 copies. In parallel, we performed a preliminary analysis of clinical notes, systematically documenting improvement events and classifying them into Features (strength, autonomy, endurance, balance) plus Domains (global, lower limbs, posture, gait).

ECG analysis. Mean Nf declined from 9.1 at baseline to 8.3 at the intermediate and 6.2 at the last ECG. The reduction became significant only at the last timepoint ($p=0.026$). Af decreased more steadily, from 0.118 at baseline to 0.082 at the intermediate and 0.077 at the last ECG, with significant reductions already at the intermediate ($p=0.037$) and persisting at the last ($p=0.017$). These changes did not differ by SMA type, sex, age, or SMN2 copy number, pointing to a general trend across the cohort.

Across 146 improvement events, the most frequent Features were autonomy (n=33), strength (n=28), endurance/fatigability (n=28), and balance (n=27). The most frequent Domains were global (n=43), lower limbs (n=18), posture (n=13), and gait (n=10). SMA2 patients more often showed axial/postural gains, while SMA3 improved in gait and upper-limb function. Over time, endurance and strength predominated in early visits, while autonomy in postural transitions emerged later. Younger children more frequently showed endurance, whereas older patients displayed strength and autonomy in complex tasks.

P13

Design and preliminary validation of a clinical outcome measure for SMA patients - SMA-LIFE ML43472 STUDY

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The introduction of new treatments has highlighted the need to evaluate aspects of spinal muscular atrophy (SMA) that conventional motor scales do not consider, also showing the limited sensitivity of current tools to detect certain changes in the disease.
This study aims to develop and validate a new multidimensional clinical tool to assess the functional status of patients with SMA.

This prospective, non-interventional study is conducted in five centers in Spain and includes patients aged 16 or older with a confirmed diagnosis of 5q SMA. A panel of neurologists, rehabilitation specialists, and patient representatives designed the clinical tool, which includes the evaluation of 53 items through a questionnaire and the measurement of clinical variables (BMI, FVC, and pinch strength). The centers administer the tool at baseline, 12 months, and 24 months, along with other conventional scales. An interim Rasch analysis was performed after the initial visit to evaluate its psychometric properties, including model fit, dependence, reliability, construct validity, and sensitivity to change.

As a conclusion, we developed and validated the SMA Life, a new clinimetric tool for assessing disease progression. This tool includes bulbar, motor, respiratory, and fatigability domains. Through Rasch analysis, we selected the best items, which demonstrated excellent reliability and construct validity. SMA Life is easy to administer and could improve patient follow-up and care by adapting to individual patient needs.

P14

A pathomechanism for spinal muscular atrophy based on dysregulated internalization of BMPR2

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Spinal muscular atrophy (SMA) is a neurodegenerative disease caused by insufficient levels of survival of motor neuron (SMN) protein and primarily affects motor neurons and their synapses. Maintenance of synapses involves bone morphogenetic protein receptors (BMPRs) and receptor levels are regulated by endocytosis. Here we describe a constitutive macropinocytotic pathway that is upregulated in motor neuron-like cells upon knockdown of SMN, in primary motor neurons from SMA model mice and in fibroblasts from an SMA patient. Macropinocytosis upregulation was phenocopied by chemical inhibition of the small GTPase cdc42 suggesting that SMN and cdc42 cooperate. A proximity screen identified cdc42 as a possible binding partner of SMN and co-immunoprecipitation of SMN with nucleotide-free cdc42 pointed to a GEF-like interaction. At low SMN levels, suppression of constitutive macropinocytosis by cdc42 was relieved resulting in enhanced BMPR2 internalization, lysosomal degradation and a severe drop in BMPR2 levels. We propose a pathomechanism for SMA that lowers the availability of BMPR2 via constitutive macropinocytosis.

P16

Risdiplam ameliorates functional performance in adult SMA 2 and 3: Results from the MFM32 and other validated outcome measures

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Risdiplam improves motor function in patients with Spinal Muscular Atrophy (SMA), especially in younger individuals. In adults, treatment typically stabilizes motor abilities,although subtle improvements are often reported, but not always captured by standard assessments. The 32-item Motor Function Measure (MFM-32), although less frequently used than other scales in routine practice, has shown a good responsiveness in detecting Risdiplam-induced changes in both paediatric and adult SMA types 2 and 3.

To evaluate the long-term safety and clinical efficacy of Risdiplam in adult SMA type2 and 3 patients followed at two tertiary Italian Centers, with a specific focus on the responsiveness and sensitivity of the MFM-32 compared to other standard motor outcome measures.

Patients underwent a comprehensive motor function assessment through Hammersmith
Functional Motor Scale-Expanded (HFMSE), Revised Upper Limb Module (RULM) and MFM-32 at baseline (T0) and after 6 (T6), 12 (T12) and 24 (T24) months of treatment. The Clinical Global Impression (CGI) scale was administered at T12 and T24 to assess patient and clinician perceptions of change.

The study included 24 adult patients (mean age 36.7 years) of which 11 non-sitter (46%), 11 sitter (46%) and 2 walker (8%). At baseline, a significant floor effect was observed for HFMSE and RULM. MFM-32 proved to be the most responsive tool, showing a significant mean improvement of +3.2 points ($p=0.0002$) and a clinically meaningful response (≥3 points) in 58.4% of the cohort. Sub-domain analysis confirmed that these improvements were driven by significant gains in MFM-D2 (proximal; +4.7, $p=0.0009$) and MFM-D3 (distal; +5.7, $p=0.0056$). While HFMSE and RULM also showed significant mean improvements, the percentage of patients with noteworthy gains at 24 months remained stable (29.2%). These objective findings were mirrored
by patient and clinician CGIs. Finally, over the 24-month observation period, Risdiplam demonstrated sustained clinical efficacy and safety with no serious adverse events reported.

MFM-32 was more sensitive in detecting minimal motor changes in severely affected adult SMA patients. CGI results aligned with MFM-32, supporting the clinical relevance of detected changes. Despite being more time-consuming, MFM-32 may be the preferable outcome measure for evaluating treatment durability and response in non-ambulant SMA type 2 and 3 patients in advanced disease stages.

P18 - FLASH TALK

Prenatal SMN-dependent defects in translation uncover reversible primary cilia phenotypes in SMA

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Spinal Muscular Atrophy (SMA) is a childhood neuromuscular disease caused by mutations in the ***SMN1*** gene, resulting in reduced levels of SMN protein. Increasing evidence reports new and unexpected phenotypes in treated type I SMA patients, including neurodevelopmental issues in some individuals. Moreover, a key challenge in SMA treatment is determining the optimal timing of intervention, as the greatest therapeutic benefits occur when treatment is administered ideally before symptom onset.
Recent work from our lab has demonstrated that SMN depletion leads to a broad spectrum of morphological and molecular disruptions in SMA mouse embryos, occurring long before symptoms appear. Additionally, SMN has been identified as a ribosome-associated protein with a fundamental role in translation and ribosome biology. However, whether this function contributes to SMA prenatal development has yet to be investigated.

We aimed to deepen the understanding of embryonic manifestations of SMA by investigating the neurodevelopmental phenotype in SMA mice ***in vivo***. Using ribosome profiling of brain and spinal cord in Taiwanese SMA mouse embryos at embryonic day 14.5, we identified widespread perturbations in translation throughout the central nervous system, particularly affecting genes involved in regulating the structure and function of primary cilia. Primary cilia are non-motile sensory organelles extending from the cell membrane, with critical roles in coordinating various signalling pathways. Dysfunction of these organelles leads to multi-systemic diseases called ciliopathies, often accompanied by cognitive impairments. In prenatal SMA mice, the density of primary cilia ***in vivo***, as well as cilial length in hippocampal neurons ***in vitro***, was significantly decreased. Proteomic analysis revealed downstream perturbations in primary cilia-regulated signalling pathways, including Wnt signalling. Meanwhile, cell proliferation was concomitantly reduced in the hippocampus.
Having identified these defects at the prenatal stage of the transgenic mouse model of SMA, we then asked whether replacing levels of SMN could rescue this primary cilia phenotype. Using the same transgenic mouse model, pregnant mice were given risdiplam orally for 5 days before analysis of primary cilia. We found that this transplacental delivery of risdiplam could restore SMN levels in the embryo, and crucially correct the primary cilia phenotype previously observed.

Our results therefore reveal that SMN is required for normal development of brain and spinal cord, with its low levels leading to defects in the translation of primary cilia genes that result in a primary ciliopathy, and that these defects can be rescued by SMN replacement therapy.

P20

Enhancing cognitive and developmental testing in children with SMA

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After the advent of disease modifying therapies for individuals with Spinal Muscular Atrophy (SMA) there has been increasing interest in determining the possible cognitive and neurodevelopmental comorbidities. To assess cognitive and developmental delay in children with SMA type I and in infants detected with newborn screening (NBS), different studies have used the assessment tools commonly adopted. The aim of this study is to reflect on the need for some adjustments to the commonly used developmental scales so as to collect reliable data in children with SMA. To accomplish this, thanks to a professional 3Dprinter and the choice of light weight 3D printing textures, we adapted some of the materials by reducing their weight and maintaining the same shape and colour of the original ones. The original test and the lower-weight version were administered to 11 children with SMA type I and to infants detected with NBS. The ability to perform the item, the fatigability and time-dependent items were assessed. Moreover, particular attention was given to maintaining a correct posture of head and trunk, placing the material in a suitable position for each individual to obtain the best visual scanning and testing the child at rest before the motor assessment evaluation to reduce the fatigue. Children with SMA with high motor impairment scored differently when using the standard protocol rather than the lower-weight version developmental scale was used. Results from children with SMA support the assumption with the reduction of weight and some adaptation to posture could offer more reliable data when testing small children with SMA. Even if no conclusion can be drawn, these findings suggest that assessment tools with a low motor/weight component should be used in this vulnerable population to estimate cognitive abilities. Larger and collaborative studies are needed to find the most appropriate tools to test these vulnerable infants with SMA.

P22

Longitudinal neurocognitive evaluation in a cohort of SMA1 pediatric patients

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Spinal muscular atrophy type 1 (SMA1) is a severe neuromuscular disorder caused by biallelic mutations in the ***SMN1*** gene. It is characterized by early onset and rapid progression of muscle weakness and atrophy. Disease-modifying therapies (DMT) have substantially altered the natural history of the disease, significantly improving both survival and motor function. In this context, understanding the neurocognitive and adaptive developmental trajectories of affected individuals has become increasingly important.

To investigate neurocognitive and adaptive functioning over a 12-month follow-up in a cohort of children with SMA1 who received early treatment with a disease-modifying therapy (DMT).

Twelve children with genetically confirmed SMA1 (mean age: 3.8 years) were evaluated at baseline (T0) and after 12 months (T1). Neurocognitive development was assessed using the ***Griffiths Mental Development III- (GMDS-3)***, while adaptive functioning was evaluated using the ***Vineland Adaptive Behavior Scales II (Balboni et al., 2016 (VABS-II)***. The GMDS-3 revealed a slight decline in the Foundations of Learning subscale (T0 Quotient Score [QS A]: 85; T1 [QS A]: 83) and in the Global Developmental Quotient (T0 [QS: 67]; T1 [QS: 62]). The Language subscale remained stable (T0 [QS B]: 88; T1 [QS B]: 88). Results from the VABS-II indicated a mild decline or trend toward stability in adaptive functioning (T0 [Deviation IQ]: 74; T1 [Deviation IQ]: 69). Overall, language abilities appeared relatively preserved, whereas learning-related skills and adaptive functioning showed areas of vulnerability.

Despite significant motor impairment, children with SMA1 demonstrated a relatively favourable neurocognitive profile, particularly in language domains. However, observed declines in learning abilities and adaptive functioning highlight potential developmental fragilities. These findings underscore the need for early, targeted interventions and continuous longitudinal monitoring, with particular attention to cognitive and adaptive domains, to optimize long-term developmental outcomes.

P24

Nutritional challenges in Spinal Muscular Atrophy under modern therapy – From dysphagia to protein requirements

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Spinal muscular atrophy (SMA) is a genetic neuromuscular disease marked by degeneration of motor neurons and resultant muscle weakness. With the advent of disease-modifying therapies, prognosis and lifespan have improved substantially. As patients live longer and with greater functional potential, managing nutritional issues becomes increasingly important to optimize response to therapy, prevent complications, and preserve quality of life.

This work aims to provide an overview of central nutritional challenges in SMA under modern therapy, with focus on swallowing difficulties (dysphagia), changes in body composition, energy and protein requirements, and practical monitoring tools such as bioelectrical impedance analysis (BIA).

In clinical practice, we have exemplarily assessed patients with SMA using BIA to evaluate body composition and nutritional status. A representative case will be presented in the poster to illustrate the practical implications of this approach.

Dysphagia remains common in SMA, particularly in patients with bulbar involvement, and can lead to inadequate intake, aspiration risk, and need for texture modifications or enteral feeding. Even with modern therapy, many patients show altered body composition—reduced lean mass, increased fat mass—due to reduced physical activity, altered metabolism, or disease severity. Protein intake emerges as a key factor: sufficient high-quality protein supports maintenance or improvement of muscle mass and may facilitate better functional outcomes. Energy requirements vary greatly depending on SMA type, respiratory support, mobility, and treatment response. Tools such as BIA allow non-invasive monitoring of body composition changes and can guide individualized nutritional interventions.

Under modern SMA therapies, nutritional management must be individualized and proactive. Key areas include early recognition and management of dysphagia, regular assessment of body composition (e.g. via BIA), tailoring protein and energy intake, and close interdisciplinary coordination. The poster will present our case example, illustrating these principles in practice.

P26

Selective protective effects of melatonin in mouse models of Spinal Muscular Atrophy

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Spinal muscular atrophy (SMA) is characterized by motor neuron loss, neuromuscular junction (NMJ) disruption, and myelin abnormalities, resulting in persistent motor deficits. While Smn-enhancing therapies exist, residual pathology remains, highlighting the need for combinatorial, Smn-independent interventions to promote motor unit regeneration. Melatonin has shown to have a potential neuroprotective effect on nerve regeneration, motor axon regeneration, as well as anti- inflammatory properties. Moreover, its ability to cross the blood–brain barrier with no significant side effects makes melatonin a promising neuroprotector.
We analyzed NMJ recovery, axon integrity, and myelin status in cranial muscles of SmnΔ7 (severe) mice and transverse abdominal (TVA) muscles of Smn2B/- (moderate) mice, as these muscles are selectively vulnerable in each model. Melatonin was administered from postnatal day 3 until end-stage. NMJ occupancy, neurofilament accumulation, and myelin integrity were assessed to evaluate compound efficacy.

In the $Smn^{2B/-}$ mouse model, melatonin improved NMJ innervation and reduced neurofilament accumulation in the transverse abdominal (TVA) muscles, demonstrating a protective effect. In the severe SmnΔ7 model, cranial muscles treated with Nusinersen already exhibited normalized NMJ innervation and neurofilament levels. Melatonin was tested to determine whether it could further prevent axon loss in these muscles; however, it provided no additional benefit. These results emphasize a model-dependent effect: melatonin protects NMJ recovery in the context of ongoing degeneration but is unable to target the post treatment deficits in axon number observed in the SmnΔ7 mouse model
Overall, this study highlights the selective regenerative potential of melatonin in SMA and underscores the importance of disease severity in shaping therapeutic responses.

P28

Effects of spinal stabilisation surgery on motor function in SMA patients receiving disease-modifying therapy

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The early loss of motor neurons in spinal muscular atrophy (SMA) results in profound trunk and limb muscular deficiency, leading to progressive scoliosis in patients during growth. The introduction of disease-modifying therapies significantly improved survival and functional outcomes; however, spinal deformity remains one of the most frequent complications of SMA.

To retrospectively investigate the effects of scoliosis surgery on motor function in SMA patients who are already receiving disease-modifying therapy (DMT).

All SMA patients treated with a DMT at the Pediatric Center of Semmelweis University between April 2018 and September 2025 who underwent spine stabilisation surgery after treatment initiation were included in the study. Motor ability assessments were performed at four-month intervals from treatment initiation during the follow-up, using the HFMSE (Hammersmith Functional Motor Scale Expanded), RULM (Revised Upper Limb Module), 6MWT (6-minute walk test) and CHOP-INTEND (The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) scales, appropriately chosen by the functional state of the patients.

Sixty-four patients initiated DMT at the Pediatric Center during the observed period. Eleven children met the inclusion criterion (n=1 SMA1, n=9 SMA2 and n=1 SMA3). All patients received nusinersen as initial therapy, although in 2 cases, treatment was later switched to risdiplam due to difficulties with the intrathecal drug administration. The mean overall follow-up time was 1020 days (±797) after the first spinal surgery. The first postoperative follow-up visit was on day 75 (± 36) after surgery; however, 3 patients were not in adequate condition to complete the movement assessments. Of the 8 patients, 7 performed worse than before, as measured by the HFMSE scale. The mean change was -8.9 points (SD 8.3). After one year, 4 out of 6 patients remained below their preoperative performance (mean change -4.2; SD 7.3). Upper limb performance (RULM) decreased in a similarly high proportion – 6 of 7 patients (mean change -3.4, SD 3) – at the first postoperative visit. It remained negative in 4 out of 6 patients after one year. Two patients were assessed with the CHOP scale, both remained below their preoperative performance. One patient was ambulant before spine surgery with a walking frame, this patient's 6MWT performance decreased from a preoperative 71.2 m to 35.2 m in one year.

The lifetime prevalence of scoliosis is expected to increase as DMTs are applied. Spinal stabilisation surgeries offer numerous benefits in terms of improving the patient's quality of life; however, children's overall motor performance declined significantly after the surgery, and in many cases their preoperative motor function was not regained even after one year.

P31

Preservation of motor units in the Gastrocnemius Muscle of SMA mice expressing the Chaperone variant Hspa8^{G470R}

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Reduced levels of survival motor neuron (SMN) protein cause Spinal Muscular Atrophy (SMA), a neurodegenerative disease characterized by profound synaptic dysfunction at the neuromuscular junction (NMJ). SMN interacts with Hspa8, a constitutively expressed molecular chaperone, enriched in neurons and at the NMJ, that plays a central role in proteostasis by promoting proper protein folding and degradation.

Expression of the synaptic chaperone variant Hspa8^{G470R} in SMAΔ7 mice suppresses most disease manifestations during postnatal and young-adult stages (3–4 months) and enhances neurotransmission in both SMA and control animals compared with the wild-type chaperone. Two mechanisms mediate this protective effect: (i) direct restoration of synaptic function through improved SNARE complex assembly, which is compromised in SMA mice expressing the wild-type Hspa8, and (ii) a small increase in SMN protein levels derived from the human ***SMN2*** gene. Whether these benefits persist throughout aging, however, remains unknown.

To address this question, we assessed neuromuscular function ***in vivo*** by electromyography (EMG) of the gastrocnemius (GN) muscle in 12–24-month-old SMAΔ7 mice. Compound muscle action potential (CMAP) recordings showed that mean maximal CMAP amplitudes (CMAPmax) were comparable across genotypes. Likewise, single motor unit potentials (SMUPs) displayed similar mean amplitudes, and motor unit number estimates (MUNE) revealed no loss of motor units in SMA mice relative to controls. During repetitive stimulation, CMAP decrement analysis detected no genotype-dependent differences. Together, these data demonstrate preserved motor unit number and size in the GN muscle of SMA Hspa8G470R mice into advanced age, with no evidence of compensatory collateral reinnervation.
Additionally, intracellular recordings from ***ex vivo*** transversus abdominis (TVA) muscle fibers—one of the most vulnerable muscles in SMA—confirmed that Hspa8G470R maintains efficient neurotransmission at the NMJ in aged SMA mice.

In summary, our findings indicate that Hspa8^{G470R} provides sustained protection against synaptic dysfunction across the lifespan of SMAΔ7 mice, supporting its role as a potent lifelong modifier of disease progression.

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Divergent therapeutic effects of risdiplam and AAV9-SMN on cerebellar pathology in severe Spinal Muscular Atrophy

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Spinal muscular atrophy (SMA) is a motor neuron disease caused by ubiquitous SMN deficiency leading to motor neuron degeneration. Available treatments significantly extend survival but only partially rescue motor function in patients. Importantly, increasing evidence suggests that neuronal circuits beyond the spinal cord contribute to the SMA phenotype and may not be effectively targeted by current therapies. The cerebellum, a brain structure essential for sensory processing and motor control, has recently been implicated in SMA. Accordingly, previous studies identified cerebellar pathology in the severe ***SMNΔ7*** mouse model. Here, we investigated whether cerebellar abnormalities are restricted to ***SMNΔ7*** mice or extend to another severe model of the disease, the Taiwanese SMA mouse. We found that Taiwanese SMA mice exhibit a strikingly underdeveloped cerebellum compared to other brain regions. The cerebellar deficits include a markedly reduced vermis, severely deformed Purkinje cells, and impaired Purkinje cell function, resulting in reduced cerebellar output. To test whether this pronounced pathology could be rescued by current SMN-inducing therapies, we treated Taiwanese SMA mice with either risdiplam or AAV9-SMN. Risdiplam treatment improved survival, motor performance, and cerebellar pathology. In contrast, AAV9-SMN prolonged survival but resulted in reduced body size, persistent motor dysfunction, and failure to rescue cerebellar defects, despite no evidence of motor neuron death, neuromuscular junction denervation, or spinal synaptic loss. These findings demonstrate that cerebellar pathology is a conserved disease feature across severe mouse models of SMA that is fully restored by systemic treatment with risdiplam but not by AAV9-SMN gene therapy, highlighting the cerebellum as a critical contributor to motor deficits and the importance of its therapeutic targeting in SMA.

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Antisense oligonucleotides treatment uncovers persistent intracellular pathways dysregulation in Spinal Muscular Atrophy motoneurons

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Spinal muscular atrophy (SMA) is a severe neuromuscular disease caused by homozygous loss or mutation of the SMN1 gene, leading to insufficient levels of the survival motor neuron (SMN) protein. Disease severity is largely influenced by the copy number of the SMN2 gene, which has a nearly identical sequence to the SMN1 gene. SMN2 predominantly produces truncated transcripts but can generate limited amounts of full-length SMN protein. Thus, SMN2 works as a disease modifier, with higher copy number correlating with milder phenotypes. Despite the existence of other SMN-independent disease modifiers, the search for therapeutic interventions has focused on strategies that increase SMN protein levels. Nusinersen, the first approved antisense oligonucleotide (ASO) therapy, exemplifies this approach by modifying SMN2 splicing to enhance the production of full-length SMN protein.

The main objective of the present work is to evaluate therapeutical effect of Nusinersen-like ASO to determine its ability to restore the cellular collapse and altered signaling pathways observed in the context of SMA. To analyze the specific impact of this strategy on motoneurons, we employed induced pluripotent stem cells (iPSCs) derived from SMA patients and differentiated them into motoneurons. In parallel, we used motoneurons isolated from the spinal cords of SMA mouse embryos.

Results indicated that treatment with Nusinersen-like ASOs promoted correction of SMN2 splicing and led to increased SMN mRNA and protein level. Beyond this molecular effect, ASO-treated motoneurons exhibited improved neurite network integrity and partial correction of dysregulated signaling pathways. However, the treatment did not prevent some of intracellular alterations observed in these cells. These findings indicate that motoneurons cultures as a robust platform to investigate therapeutic mechanisms and highlight the need for combinatorial approaches to fully address the complex cellular pathology of SMA.

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HINALEA 2: Baseline observations in a trial evaluating risdiplam in patients with SMA who experienced a plateau or decline in function after gene therapy

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The HINALEA 2 trial (NCT05861999) is an open-label, single-arm, multicentre clinical trial evaluating the safety and efficacy of risdiplam administered in paediatric patients with spinal muscular atrophy (SMA) and two survival of motor neuron 2 (*SMN2*) gene copies, who have previously received onasemnogene abeparvovec and are experiencing a plateau or decline in function.

This trial includes paediatric patients <2 years of age who have received onasemnogene abeparvovec either pre- or post-symptomatically. Eligible patients must have experienced a plateau or decline in swallowing ability and at least one additional function/ability, such as respiratory or motor function, per the appropriate expectation as evaluated by a clinician. The duration of the plateau or decline should have been for ≤6 months and documented at two individual time points.

The 72-week primary analysis will include assessment of the Oral and Swallowing Abilities Tool (OrSAT), the change from baseline in the raw score of the Bayley Scales of Infant and Toddler Development, third edition (BSID-III) Gross Motor Score and the Peabody Developmental Motor Scales, third edition (PDMS-3).

The objective of this report is to describe the baseline clinical characteristics of the initial enrolled paediatric patients in the HINALEA 2 trial. The identified parameter of decline or plateau for each patient and the length of time from onasemnogene abeparvovec administration to these events as well as clinical swallowing assessments at baseline will be reported.

HINALEA 2 is currently enrolling at multiple sites globally. Final results are expected to provide important information on the safety and efficacy of risdiplam treatment after onasemnogene abeparvovec gene therapy.

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Defining the clinical benefits of disease-modifying therapy in people living with spinal muscular atrophy who are permanently ventilated: A UK-based Delphi consensus process

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Disease-modifying therapies (DMTs), including nusinersen and risdiplam (***SMN2***-targeted therapies) and onasemnogene abeparvovec (***SMN1*** replacement therapy), have significantly improved outcomes for people living with spinal muscular atrophy (SMA). In the UK, access to DMTs is restricted for those who require permanent ventilation (PV; defined as tracheostomy or ventilatory support for at least 16 hours per day for 21 consecutive days without acute reversible infection). Fewer than 20 individuals with SMA who are receiving PV (SMA-PV) currently have access to ***SMN2***-targeted therapies through UK compassionate schemes. A modified UK-based Delphi consensus process was initiated to assess the clinical benefit DMTs may offer to people living with SMA-PV and to generate evidence-based best-practice recommendations.

A UK-based expert panel of 19 neurologists and respiratory consultants, experienced in managing individuals with SMA or SMA-PV, was appointed. After a targeted literature review, a questionnaire to capture clinical management and ethical considerations related to DMT use in individuals with SMA or SMA-PV was developed for all panel members to complete. Their responses have been utilised to generate 22 statements on disease-related themes. These statements have been voted on anonymously using a 6-point Likert scale, response rate was 100%, and consensus has been reached in two voting rounds. In order to capture the voice of those affected by SMA a non-voting patient advisory panel reviewed statements at each round and provided anonymised feedback for consideration by the steering committee.

It is hoped that these insights will enhance access to DMTs in the UK, guide clinical decision-making practices concerning DMT use and improve treatment outcomes for this underrepresented group of individuals.

P45

Adult SMA REACH: A comparative UK real world data study to assess the safety and efficacy profiles of Nusinersen and Risdiplam in adults with SMA

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Advancements in treatment options aimed at modifying disease progression in SMA in recent years have been made, with the introduction of drug treatments Nusinersen and Risdiplam. There has been a reported improvement in motor and pulmonary function tests in SMA patients post-Nusinersen treatment based on real-world observational data. Similar results have been observed for Risdiplam with benefits maintained for up to 2 years post treatment initiation. There have been limited studies directly comparing Nusinersen and Risdiplam in patients with SMA, especially in UK cohorts. Most studies have focused on evaluating each drug individually in clinical trials or real-world settings, but comparative analyses are limited in adults. Adult SMA REACH is a multi-centre longitudinal observational data collection study that collects RWD during routine clinical visit across 18 different sites in the UK. The study includes patients aged ≥16 years with genetically confirmed 5q SMA. Utilising data collected from the 460 patients enrolled in this study, we aim to perform an analysis comparing the efficacy and safety profiles of both interventions within the UK adult SMA population, while also identifying correlations with clinical phenotype, non-SMA medications, and patient-perceived benefits as well as identifying differences in the treated cohorts. The primary objective is to assess the efficacy and safety of Nusinersen and Risdiplam in adults, focusing on the following areas:

- Changes in functional assessments will be derived from functional scales such as RHS, ATEND, HFMSE, EK2, RULM, WHO and 6MWT.
- Changes in respiratory outcomes including FVC and PCF.
- Analysis of safety profiles based on the frequency of adverse events recorded during treatments

Baseline and follow-up visit scores will be summarised using descriptive statistics for safety and efficacy profiles. Repeated measures ANOVA will be used to evaluate changes in functional assessments and respiratory outcome over time. Subgroup analysis will be performed to compare outcomes by SMA type, SMN2 copy number, and functional status. Chi squared tests will be used to compare frequencies of adverse events between subgroups (SMA type, functional status, interventions, SMN2 copy number). The data presented will represent the first direct comparison of these treatments in the adult UK population using real-world evidence, and aims to compare the efficacy and safety profiles of both interventions within the UK adult SMA population providing critical insights that will support improved patient outcomes and inform future treatment decisions.

P47

Early motor and musculoskeletal outcomes of presymptomatic SMA infants treated with gene therapy in Sweden

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Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder caused by mutations in the SMN1 gene, resulting in a deficiency of the survival motor neuron (SMN) protein. Disease severity is influenced by the number of SMN2 gene copies. Significant and often irreversible motor neuron loss occurs before symptom onset, emphasizing the critical need for early medical intervention. Newborn screening (NBS) for SMA was implemented in Sweden in 2023, enabling presymptomatic identification and medical treatment of affected infants.

This study describes early motor development, musculoskeletal outcomes, and treatment responses in presymptomatically identified infants with SMA treated with gene therapy.

Infants with biallelic mutations in SMN1 and up to 3 copies of SMN2 identified through NBS, were enrolled after parental consent. All participants received onasemnogene abeparvovec-xioi (Zolgensma), with temporary administration of risdiplam (Evrysdi) prior to gene therapy. Infants were assessed by a multidisciplinary team at diagnosis and every three to six months until two years of age. Outcome measures included motor function (CHOP-Intend, Bayley-III), joint range of motion, spinal and postural assessment, and monitoring for treatment-related complications.

Early observations suggest that presymptomatic treatment supports acquisition of age-appropriate motor milestones, with minimal musculoskeletal complications within the first years of life.

This study provides the first Swedish data on presymptomatic SMA infants treated with gene therapy. Early medical intervention appears to positively influence motor development and mitigate secondary musculoskeletal complications. These findings improve understanding of disease phenotype in presymptomatic SMA and guide proactive care. Detailed longitudinal data are necessary to evaluate overall neuromuscular development and inform anticipatory care.

P49

Motor function changes in SMA types 1 and 2 during risdiplam treatment

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Spinal Muscular Atrophy (SMA) is caused by the loss of function of the survival motor neuron 1 (SMN1) gene resulting in deficiency of intracellular SMN protein and is characterised by progressive motor function loss. While efficacy of SMN2 splicing modifiers (i.e., nusinersen and risdiplam) has been shown in clinical trials in infants, children and young adults with SMA, efficacy has not been investigated in severely affected adult patients with longstanding disease. However, treatment evaluation of risdiplam is particularly relevant for this population, as risdiplam is often the only treatment option due to reimbursement restrictions (e.g., age or weight) or disease severity (e.g., severe scoliosis or scoliosis surgery).

In this observational cohort study, we aimed to assess motor function changes in adults with SMA type 1 and 2 with longstanding disease and severe motor function impairment during treatment with risdiplam.

We longitudinally evaluated motor function during treatment with risdiplam up to 36 months by using motor function scales and patient reported outcome measures.
Findings We included 76 treatment-naïve patients (median age 27; range 11-52 years) with SMA types 1 and 2, of whom 93% (n=71) was above 18 years at treatment initiation. We treated patients for a median of 35 months (range 1–40). Median revised upper limb module (RULM) scores remained stable up to 36 months, with a score of 6 (IQR 2–15) at baseline and 6 (IQR 2–14) after treatment; we observed stabilised or improved RULM scores in 60% (n=37) of patients. In addition, 90% (n=53) of patients self-reported stability or improvement in overall well-being on the Patient Global Impression of Change (PGIC) scale after more than 36 months of risdiplam treatment. Treatment with risdiplam was generally well tolerated and we did not identify new safety concerns. Seven patients (9%) discontinued treatment due to the burden of hospital visits or side effects outweighing the perceived benefit of treatment. One patient (1%) discontinued due to perceived motor function decline. Five people (7%) died during follow up, of which none were related to treatment with risdiplam.
We present motor function score changes in older patients with SMA types 1 and 2 during prolonged treatment with risdiplam. The motor function trajectories of patients with SMA types 1 and 2 with severe motor impairment differ from the progressive motor function decline described in natural history studies. In addition, the majority of patients self-reported improvement or stabilisation in motor function and overall well-being.

P51

When is it too late to treat someone with the Spinal Muscular Atrophy type 3a? Analysis of the CUIDAME Spanish registry

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Compared to other severe forms, the SMA type 3a population has historically been underrepresented in disease-modifier treatment (DMTs) clinical trials. Given the increasing evidence that early treatment is crucial for achieving better outcomes, we consider it essential to study whether early treatment in this population can assess the maintenance of acquired motor milestones.

This study assessed patients classified as Type 3 in the medical records, with onset age between 18 and 36 months, included in the national Spanish registry for SMA (CUIDAME), and signed informed consent. Participants were stratified into three groups based on the age at which they started treatment: patients treated before the age of 4 (Early Treatment: ET), after the age of 4 (Delayed Treatment: DT). The third group was the Natural History (NH) group, in which data were obtained from patients who were never treated or data collected prior to the initiation of DMT.

There are 110 subjects already registered as type 3a (11 ET, 18 DT and 81 NH) with a median (q1, q3) onset age of 18 m (14, 24) ET; 22 m (17, 24) DT and 21m (15, 24) NH. Females were 82% ET, 44% DT, 56% NH. The percentage of the population with 3 ***SMN2*** copies was the most prevalent (73% ET, 67% DT, 61% NH). Mean age at start of treatment was 2.6 y in the ET group and 6.7 y in the DT group. Median age (q1, q3) of sitting without support acquisition among the groups were 6.97 m (6.05, 7.03) ET, 6 m (5.95, 6.99) DT, and 8.05 m (7.03, 14.25) NH. Only the NH reported losses in seating capacity. Regarding walking without support, NH median age gained (q1, q3) was 14.98 m (11.99, 20.99), and 75% (n=61) lost the capacity, 30% (n=19) of them did so before the age of 8. DT gained walking at a median age of 15.01m (12.98, 18.02), and 39% (n=7) had already lost the capacity. This group's mean age at last visit was 11.3 y (4.6-15.9). The ET gained walking at a median age of 15.05 months (13.52, 17.99). After that, two participants lost the ability to walk before starting treatment, but regained it after the initiation of a DMT. Thus, with a mean age of 6.3 y (2.8-9.2)at the last visit, all patients retained the ability to walk. Motor scales and other clinical variables will be presented.

Further research is needed to identify prognostic factors that may modify therapeutic response in these patients. This knowledge is essential to manage expectations better, particularly regarding the maintenance or possible recovery of ambulation depending on the age at the start of treatment, and to clarify the real impact of therapies in this subgroup.

P53
Intrathecal lumbar catheter and port system for Nusinersin administration in SMA: Experience from 2 UK centres

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An intrathecal lumbar catheter and subcutaneous port system is an alternative method of delivering Nusinersin treatment in SMA. This is particularly relevant for individuals in whom intrathecal access via lumbar puncture is challenging or precluded by factors such as complex spinal anatomy, spinal instrumentation or obesity. Although not yet licensed, its use has been reported in several centres across Europe and the US. In the UK, the port system has been used at an adult centre in Sheffield and a paediatric centre in Leeds to facilitate delivery of Nusinersen to some individuals who would otherwise be unable to receive Nusinersin.

This study aims to evaluate the procedural success, safety and adverse event profile of the port system in individuals with SMA who have undergone the procedure in the two UK centres.

A structured data collection tool was used to retrospectively collate information on baseline SMA characteristics, spinal history, clinical indications for port implantation, surgical details, Nusinersin dosing via the port, complications, and patient satisfaction.

A total of 10 patients were included: six adults (median age at port implantation 23.5 years, range 16-41) and four children (median age 14 years, range 12-15). Six patients had SMA type 2 individuals, and four had SMA type 3. Seven patients had severe kyphoscoliosis, and three had moderate kyphoscoliosis. Port implantation was successfully completed in eight patients. The procedure was discontinued in one adult due to an unexpected focus of infection at the surgical site, and in one child due to unsuccessful implantation despite several attempts. All but one patient underwent the procedure under general anaesthesia. The cumulative duration of port system use was 21.1 years, with a mean duration of 2.6 years per patient. A total of 82 Nusinersin doses were successfully administered via the port. Adverse events included technical issues (port flipping, access difficulties, catheter blockage/migration etc; n=8), pain (n=4), prolonged hospital stay/re-admission, (n=4), cerebrospinal fluid leak (n=3), low-pressure headache (n=3), chest infection (n=2), port infection (n=1, resulting in removal), and spinal haematoma (n=1). More than half of the adverse events (65%) occurred within the first month, and 88% within the first six months. Patient satisfaction was rated as very or somewhat satisfactory in 75%.

The port system represents a feasible method for delivering Nusinersen. Adverse events mostly occurred within the first month following implantation. Technical issues are not uncommon and establishing a protocol for their management may be helpful. Overall, the port system can be considered a viable option for selected patients in whom Nusinersen delivery would otherwise be challenging. Longer-term data are needed to evaluate its durability and sustainability.

P55
Successful management of SMA Type 1 with gene therapy and rescue nusinersen following a severe adverse event

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Spinal muscular atrophy (SMA) is a genetic disorder caused by biallelic mutations in the SMN1 gene, which encodes the survival motor neuron (SMN) protein, essential for motor neuron function and survival. Insufficient levels of SMN protein lead to progressive degeneration of motor neurons in the brainstem and spinal cord, resulting in progressive muscle weakness. The severity of SMA is primarily determined by the number of copies of the SMN2 gene, which produces only 10% of functional SMN protein. Currently, three therapeutic options address the underlying SMN protein deficiency in SMA:
(1) gene replacement therapy (onasemnogene abeparvovec), and (2) two treatments that enhance SMN2 gene splicing to increase SMN protein levels—nusinersen, an intrathecally administered antisense oligonucleotide, and risdiplam, an orally administered small-molecule splicing modifier.

To report a case of successful management of SMA type 1 with gene therapy, followed by rescue treatment with nusinersen in the setting of a critical medical deterioration.

This report describes the clinical course of a female infant diagnosed with SMA type 1 at 1.5 months of age, when she presented with progressive feeding difficulties, hypotonia, and muscle weakness.
Genetic testing confirmed a homozygous deletion of exons 7 and 8 of the SMN1 gene and the presence of two copies of SMN2. She required nasogastric tube feeding, and her CHOP INTEND score was 9/64.
She received gene therapy (onasemnogene abeparvovec) at 2 months of age. One month later, she developed sepsis and respiratory distress due to a urinary Escherichia coli infection, leading to clinical deterioration requiring intubation and mechanical ventilation. Given the severity of her clinical condition and while the therapeutic effect of gene therapy was not yet evident, nusinersen was initiated as a rescue measure to provide a more immediate enhancement of SMN protein production during this critical phase.
Her clinical course improved significantly, allowing for extubation one week after initiating nusinersen.
She completed four doses of nusinersen, during which her respiratory status remained stable, and she showed notable clinical recovery. Four months later, her CHOP INTEND score improved to 27/64, and she regained the ability to feed orally.

This study suggests that in SMA patients who, despite gene therapy, experience severe acute
functional deterioration, additional therapeutic modalities aiming to enhance SMN protein levels may be considered.

P57
Intermittent prednisolone administration ameliorates neuromuscular phenotype and extends survival of a mouse model of SMA

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5q-Spinal Muscular Atrophy (SMA) is a neurodegenerative disease caused by deletions or mutations in the Survival Motor Neuron 1 (SMN1) gene, leading to insufficient SMN protein expression. Notably, the number of copies of the homologous gene SMN2 starkly modulates the severity of the disease, which ranges from being the first cause of mortality from genetic cause in children below 3 years of age, to muscular weakness and tremors appearing in the adulthood. This evident gene dosing effect posed the rationale for the development of three therapies, all aiming at raising the expression of SMN, and introduced in the clinical practice in the last few years. Although these agents have irrevocably rewritten the natural history of SMA, they cannot be considered the ultimate cure for the disease. In addition, they suffer from high costs, side effects and invasive route of administration. Thus, it is imperative to identify and quickly translate into the clinical practice new therapeutic agents for a more thorough control of SMA symptoms. To this end, we envisioned that a drug repurposing approach might be the most effective strategy and we therefore turned our attention to the common anti-inflammatory and immunosuppressive drug prednisolone, due to its favourable effects on the phenotype of the Taiwanese and the Smn2B/– mouse models of SMA (Walter et al, EBioMedicine, 2018). Here, we aimed at extending those findings to the another mouse model of SMA, i.e. the Grm7Tg(SMN2)89Ahmb Smn1tm1Msd Tg (SMN2*delta7)4299Ahmb/J line, commonly known as the SMNΔ7 mice, and extensively used for proof-of-principle preclinical studies. Specifically, we applied an intermittent oral dosing of the mice from postnatal day 1 (PN1) and we monitored their welfare though daily recording of their survival and body weight growth. In addition, we administered a battery of behavioural tests starting at PN2, namely the righting reflex, the tail suspension, the tube test and the negative geotaxis test. Importantly, the comparison of the mice receiving prednisolone with those administered with the vehicle revealed a significant extension of the lifespan of treated mice (18.4+4.5 days vs 14.8+3.7 days of mice receiving vehicle only), a greater increase of body weight and an improved performance in the righting reflex and in the tail suspension tests.

In conclusion, our findings reinforce the rationale of using prednisolone as therapeutic agent in SMA patients.

P59
Boosting BDNF in SMA mouse muscles enhances the impact of SMN upregulation

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Restoration of SMN in mouse models of SMA results in well-known improvements in the disease phenotype; this includes enhancement of neuromuscular junction (NMJ) connectivity, often with the majority of endplates appearing to be fully occupied. However, even when therapies are delivered early, recovery is incomplete – as evidenced by clear loss of axons and a reduced total number of NMJs, which becomes more prevalent with a delay in treatment. This indicates that there is the possibility to enhance functional recovery following administration of SMN-enhancing drugs.
We have recently shown that administration of the neurotrophin, brain-derived neurotrophic factor (BDNF), into the muscles of two different mouse models of Charcot-Marie-Tooth disease is able to fully restore deficits in ***in vivo*** axonal transport of signalling endosomes. Furthermore, an adeno-associated virus (AAV) that persistently and selectively boosts BDNF within muscles (AAV8-tMCK-BDNF) is able to rescue additional features of neuropathy. In unpublished mouse work, we have identified that BDNF also has therapeutic potential in spinal and bulbar muscular atrophy, while others have identified impaired BDNF signalling at distal motor nerve terminals of SMA mice.
In this study of SMA mice, we assessed the effectiveness of several different treatments, including AAV8-tMCK-BDNF, to act in synergy with an SMN-enhancing antisense oligonucleotide (ASO) to ameliorate distal motor unit pathology. ***SMNΔ7*** mice received intracerebroventricular ASO injections at postnatal day 2 (P2), followed by additional individual treatments beginning at P3, including intraperitoneal administration of AAV8-tMCK-BDNF.

None of the assessed accessory treatments had an effect on the weight or motor phenotype of ***SMNΔ7*** mice compared to nusinersen alone. As expected, the ASO by itself caused all remaining NMJs to be fully innervated, meaning there was no persistent innervation deficit for additive treatment to impact. However, analysis of intramuscular motor axons revealed that treatment with BDNF was able to increase axon number in several different cranial muscles compared to ASO only-treated muscles. This increase was associated with a decrease in motor unit size back towards wild-type levels.
Overall, these data indicate that boosting BDNF within SMA muscles has the potential to offer synergistic benefit to the distal motor unit when administrated with SMN up-regulating therapy.

P61

Embryo-targeted risdiplam therapy: Effects of prenatal-only exposure to SMN-dependent therapy in a mouse model of SMA

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Disease modifying therapies have transformed the therapeutic landscape for Spinal Muscular Atrophy (SMA). Significant evidence from clinical trials and real-world data indicate early treatment is beneficial for therapeutic outcome in patients with SMA. In patients treated with a disease modifying therapy, those treated early have the greatest therapeutic outcomes. While promising, this early post-natal treatment fails to cure the disease and does not address in utero pathologies of severe type 0 patients, which include degeneration and cell death leading to reduced foetal movement. Risdiplam is a small molecule *SMN2* splicing modifier that is orally administered, and therefore maternal delivery offers a non-invasive route to target foetal disease. Recently, a report described administration of risdiplam to one human foetus with SMA demonstrating an apparent ameliorating effect on the disorder. However, there is an absence of comprehensive preclinical data to validate this approach. We have investigated this novel therapeutic strategy in the SMNΔ7 severe mouse model. By restricting risdiplam exposure to the embryo and terminating treatment at birth, we have been able to isolate and assess therapeutic effects attributable solely to embryo exposure. Our results demonstrate oral gavage of risdiplam to the dam during pregnancy does not impact dam health. SMN**Δ**7 mouse weight, motor function and survival are significantly increased following maternal transfer of risdiplam. SMN protein levels remained elevated in the livers of SMA mice beyond postnatal day 35. Early embryonic exposure to SMN also rescued motor neuron survival and muscle atrophy, but neurofilament light chain levels remained augmented despite treatment. Neuromuscular junction pathology, possible brain abnormalities and cognitive performance are under investigation. Our research suggests that targeting SMN therapy to the embryo can postpone disease onset, yet sustained benefit likely depends on a combined prenatal and postnatal therapeutic strategy.

P63

A novel therapeutic candidate for Spinal Muscular Atrophy identified through drug repositioning: Evidence from a mouse model and patient-derived cells

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Spinal Muscular Atrophy (SMA) is a severe neuromuscular disorder caused by ***Survival Motor Neuron 1*** (***SMN1***) gene mutation, leading to reduced SMN protein levels and progressive motor neuron (MN) degeneration. The homologous gene, ***SMN2***, due to incorrect splicing, fails in rescue SMA phenotypes. Some limitations of current therapies still claim the research for new approaches aimed at increasing SMN levels. As identified through a screening of FDA-approved drugs, the antipsychotic GT5 (code name) emerged as a potent enhancer of ***SMN2*** transcript expression and splicing across multiple disease models. Using the delta 7 SMA mouse model**,** we assessed the therapeutic effects of GT5 administration on survival, motor function, neuroprotection, and neuroinflammation, by histological, molecular and RNA-seq analyses of spinal cord and muscle samples. Compared to untreated condition, GT5 treatment increased lifespan (+15%) and improved motor performance in SMA mice, upregulated SMN expression in spinal cord (≥50%) and muscles (≥1-fold), reduced MN loss (cleaved caspase-3 apoptotic marker levels: ≤63%; MN density ≥90%), and attenuated neuroinflammation by decreasing GFAP signaling (≤37%) and modulating microglial activation. Moreover, GT5 enhanced neuromuscular junction integrity and muscle trophism, suggesting additional peripheral benefits. Notably, RNA-seq analysis of GT5-treated spinal cords revealed extensive splicing changes, including direct SMN target transcripts, supporting enhanced SMN activity. We also evaluated GT5 efficacy in human SMA models using co-cultures of patient iPSC-derived MNs and myotubes, and observed enhanced MN survival and increased SMN expression, consistent with both SMN-dependent and neuroprotective mechanisms. Given its central nervous system penetrance and existing clinical approval, GT5 emerges as a promising candidate for SMA therapy, warranting further dose-optimization and preclinical validation to explore its translational potential.

P65
Goal Attainment Scaling (GAS): A patient-centred outcome in SMA

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It is a challenge to capture clinically meaningful intervention effects in (rare) diseases is due to the heterogeneity between patients, small sample sizes, and the lack of knowledge on the minimal important change (MIC) of traditional functional scales. The Goal Attainment Scale (GAS) is a patient-centred tool to evaluate the achievement of individualized goals on a five-point scale ranging from -2 (much less than expected) to +2 (much more than expected). GAS is highly appreciated in clinical care, but its suitability as an endpoint in clinical trials has not yet been established. The primary aim of this study is to evaluate the reliability, validity and responsiveness of GAS in patients with neuromuscular diseases. Our second aim is to develop an international training program for GAS evaluators.

- A systematic review to assess the current level of evidence on the psychometric properties of GAS
- Development of GAS methodology based on review findings, expert opinion and panel discussions
- Implementation and validation of GAS within clinical trials and observational studies in neuromuscular diseases including Spinal Muscular Atrophy (SMA), Congenital Myopathy (CM) and Demyelinating Polyneuropathy (CIDP).

The systematic review included 46 studies evaluating the reliability, validity and responsiveness of GAS. Results will be presented in March. Based on preliminary findings and expert input, standardized guidelines for the use of GAS are being developed. In our first randomized controlled trial, patients with SMA and CM follow a 14-week individualized progressive resistance training program. GAS ensures the individualization of exercises within this program and serves as a key secondary outcome measure. To date, 19 goal-setting and -evaluation interviews have been completed in patients with SMA. The goals identified so far target upper-extremity function and include activities such as throwing a ball into a basket at school, performing facial care, washing hair, passing plates at the dinner table, grasping objects, and making transfers with more ease.

The first steps have been taken in the validation of GAS as a meaningful personalized outcome measure for rare neuromuscular diseases, such as SMA.

P67

The SOLAR study: Phase 3 study to evaluate the efficacy and safety of salanersen in participants aged 15–60 years with Spinal Muscular Atrophy (SMA)

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Salanersen (BIIB115) is an investigational, intrathecally administered antisense oligonucleotide with novel modification to the backbone and similar mechanism of action but higher nonclinical potency than nusinersen, which enables the potential to maximize clinical outcomes with once yearly dosing. The SOLAR study is an open-label, Phase 3 study designed to investigate the efficacy and safety of salanersen in participants aged 15–60 years with spinal muscular atrophy (SMA). The study includes two cohorts (participants who are treatment-naive and those who have previously received risdiplam), and the study eligibility criteria includes a baseline Hammersmith Functional Motor Scale – Expanded (HFMSE) total score of between 10 and 54 in order to allow any decline or improvement in function to be possible to observe in all participants. All participants will receive salanersen 80 mg by intrathecal lumbar puncture every 12 months for up to approximately 5 years. The primary efficacy endpoint will be change from baseline in HFMSE total score at 12 months of follow-up in the treatment-naive cohort, based on the progressive decline expected in this population without treatment. Key secondary efficacy endpoints will be evaluated in both cohorts and include change from baseline and responder analyses in HFMSE total score, Revised Upper Limb Module (RULM) total score, and 6-minute walk test (6MWT) distance. Other efficacy endpoints include compound muscle action potential (CMAP), respiratory function, bulbar function, fatigability, and activities of daily living assessed over the study period. Additionally, safety, tolerability and pharmacokinetics of salanersen will be evaluated. Data from the SOLAR study may help inform both initiation of therapy and transitions between therapies in clinical practice.

P69

Exploring higher doses of nusinersen in Spinal Muscular Atrophy: Integrated results from the DEVOTE Part B and ONWARD studies

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DEVOTE (NCT04089566), a 3-part, Phase 2/3 trial, and ONWARD (NCT04729907), an ongoing Phase 3 open-label long-term extension study of DEVOTE, were designed to evaluate an investigational higher-dose nusinersen regimen (two 50 mg loading doses 14 days apart, followed by 28 mg maintenance doses every 4 months) in participants with spinal muscular atrophy (SMA).

The pivotal Part B cohort enrolled treatment-naive infantile-onset participants (n=75) randomized (2:1) to receive the 50/28 mg regimen or the currently approved 12/12 mg regimen. A prespecified matched sham control group from ENDEAR (NCT02193074) (n=20) served as the primary comparator for the 50/28 mg regimen (n=50).

Participants receiving the 50/28 mg regimen (baseline mean Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders [CHOP-INTEND] score: 20.9) showed statistically significant improvement over the matched sham comparator (baseline mean CHOP-INTEND: 23.6) on the primary endpoint of change in CHOP-INTEND from baseline to Day 183 (least-squares mean, +15.1 versus −11.1; least-squares mean difference [95% confidence interval (CI)]: 26.19 [20.7, 31.7]; joint-rank test least squares mean, 42.9 versus 16.9; difference [95% CI]: 26.06 [17.9, 34.2]; $p < 0.0001$). Results favored the 50/28 mg regimen relative to sham across secondary endpoints (Hammersmith Infant Neurological Examination – Section 2 [HINE–2], plasma neurofilament light chain [NfL] levels, event-free survival, and overall survival). Results also trended in favor of the 50/28 mg regimen over the 12/12 mg regimen for key biomarker and efficacy measures. Supportive data from Part B also demonstrated the benefit of the 50/28 mg regimen in treatment-naive later-onset participants. The 50/28 mg regimen was generally well tolerated, with adverse events broadly consistent with the 12/12 mg nusinersen regimen.

As of the interim data cutoff, ONWARD has enrolled 35 participants from the Part B infantile-onset cohort and 23 participants from the Part B later-onset cohort. The primary endpoint is to evaluate the safety and tolerability of longer-term treatment with the 50/28 mg nusinersen regimen. Nusinersen 50/28 mg was generally well tolerated. Pre-dose evaluations of ONWARD Day 1 for CHOP-INTEND and HINE-2 in the infantile-onset cohort, and for Hammersmith Functional Motor Scale – Expanded and Reduced Upper Limb Module in the later-onset cohort, showed consistent trends compared to DEVOTE. Collectively, these data show the longer-term efficacy and safety of the 50/28 mg nusinersen regimen.

P71

Phase 1 interim results evaluating the safety, tolerability, pharmacokinetics, and exploratory efficacy of Salanersen (BIIB115): An antisense oligonucleotide for Spinal Muscular Atrophy

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Salanersen (BIIB115) is an investigational, intrathecally administered antisense oligonucleotide with novel modification to the backbone and similar mechanism of action, but higher potency, than nusinersen in nonclinical studies, enabling the potential to maximize clinical outcomes with dosing only once yearly. This Phase 1 study (NCT05575011/EU CT 2023-505643-39) is evaluating the safety, tolerability, pharmacokinetics, and exploratory efficacy of salanersen. Part B evaluates open-label salanersen (40 mg or 80 mg doses) in pediatric participants (aged 0.5–12 years) with spinal muscular atrophy (SMA) previously treated with onasemnogene abeparvovec with suboptimal clinical status. Study objectives are to evaluate the safety and tolerability (primary) and pharmacokinetics (secondary) of salanersen. Exploratory objectives include assessment of neurofilament levels, World Health Organization (WHO) motor milestones, and motor function scales. An interim analysis was performed once the older participants in the 40 mg dose cohort (n=8) had completed at least 1 year of follow-up. Salanersen was generally well tolerated at the 40 mg and 80 mg dose levels. In participants with elevated baseline plasma neurofilament levels, salanersen treatment was associated with a 70% reduction by Day 180, which was sustained over time. Of the 8 participants with 1-year follow-up available, 4 (50%) achieved new WHO motor milestones beyond what would be expected based on baseline functional status and time on previous treatment, and clinically meaningful improvements were observed on Hammersmith Functional Motor Scale – Expanded (mean +3.3-point improvement) and Revised Upper Limb Module (mean +5.3-point improvement). The interim results of this study will inform the design of planned registrational trials in SMA.

P73
High-frequency rTMS targeting lower motoneuron circuits in SMA: interim safety, tolerability and efficacy results from STIM-SMA

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Lower motoneuron insufficiency is a leading cause of functional limitations in SMA. According to general physiological law, the study assumes that a certain level of motoneuron activation can "train" or enhance their compensatory mechanisms and increase their viability. The rationale also assumes that high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) can provide a more targeted and precise dose of activation compared to other interventions. It is worth mentioning as well that not all SMA patients have access to recent drugs with proven efficacy, and in those who do, this efficacy is sometimes modest. STIM-SMA (NCT06977269) is an interventional, open-label study evaluating the safety and tolerability of HF-rTMS in persons over 12 years old with 5q-SMA.

To report interim safety, feasibility, and describe changes in prespecified functional outcomes at an early data cutoff, we analyzed complete datasets of 9 patients. The last patient in the group finished the final examination on 20-SEP-2025; the first one started on 14-MAY-2025.

Participants: ages 12–24 years, mean 17.44 ± 4.77 years; 3 with SMA type III, others type II; 2 girls, others boys.

Safety: there were no AEs at all; only 1 case of a mild respiratory infection at the very beginning of the intervention, which did not affect daily activity. There were no discontinuations, interruptions, or other protocol deviations.
Exploratory outcomes: except for 2 cases, after 2 weeks of treatment all participants showed at least a 1-point improvement on either MFM or RULM; 1 patient achieved a 2-point improvement on HFMSE as well. Improvement was absent in the strongest type III female and the weakest type II male. However, the weakest patient was highly satisfied due to positive autonomic signs dynamics and a subjective feeling of greater endurance.

Interim findings indicate good tolerability and feasibility of HF-rTMS in SMA, with early descriptive signals of functional improvement in most participants; continued enrollment with broader patient heterogeneity will clarify the scope of benefit and the most promising target population.

P75

Innovating respiratory care for children with SMA: Improving effectiveness and compliance of respiratory muscle training through gaming

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Spinal muscular atrophy (SMA) can cause respiratory muscle weakness, often already during childhood. Expiratory muscles are typically more severely affected than inspiratory muscles, as the diaphragm is relatively spared. Inspiratory muscle weakness may nevertheless lead to hypoventilation, while expiratory muscle weakness can impair cough strength. As a result, patients may experience symptoms of nocturnal hypoventilation and become more susceptible to respiratory infections, which may trigger a cycle that ends in respiratory insufficiency.

Respiratory muscle training (RMT) is a therapy that aims to improve respiratory muscle function, i.e. strength and endurance and ultimately to delay the use of mechanical ventilation and to lower the risk of respiratory infections and hospitalizations. RMT typically involves the use of a small device that provides adequate resistance, thereby increasing the load on the respiratory muscles in an attempt to mobilize plasticity of skeletal muscles.

We previously explored the efficacy of RMT in SMA (RESISTANT study, Kant et al., 2025) that showed promising results, high acceptance rates of the training schemes, but nevertheless suboptimal adherence even in motivated patients. The lack of compliance seems an important obstacle for RMT and achieving its goals. Although patients often indicate that they value RMT, it also represents yet another tedious routine in a packed agenda.

We hypothesized that the acceptability of RMT in children with NMD may be enhanced by integrating a game-based approach that would add fun to the routine. Designing such a game for a heterogeneous group in terms of age and gender is challenging. We identified key requirements, including live feedback for both child and clinician, and accessibility through Android and iOS. To increase long-term engagement, features such as streaks, leaderboards, and a store will be implemented, examples of which will be shown during the conference.

We furthermore aim to include the game-approach in a randomized controlled trial that is planned to start in Q1 2026 and aims to evaluate the role of RMT in children with an NMD. Efficacy will be assessed after 6 weeks, and feasibility after 6, 12, and 24 weeks.

P77

Study protocol for the MAGNITUDE study: A randomized controlled trial to investigate the effects of personalized progressive resistance training in patients with SMA and CM

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Physical exercise training may slow disease progression or even enhance muscle strength in patients with neuromuscular diseases. Yet, the efficacy of personalized progressive resistance training (PRT) on muscle function and functional activities remains largely unknown.

We designed a multicenter, single-blinded, randomized controlled trial to determine the effect of personalized PRT of the upper extremities. We aim to include a total of 54 patients with spinal muscular atrophy (SMA) or congenital myopathy (CM) aged 10-50 years in the Netherlands. Participants are randomly assigned to the intervention group following a PRT program, or a delayed intervention group. PRT will consist of supervised personalized strength- and power exercise training three times per week, for the duration of 14 weeks. The primary outcome is the mean difference in maximal force (Newton) of isometric muscle strength of elbow flexors after 14 weeks of PRT and usual care. Secondary outcome measures are functional, electrophysiological, morphological, metabolic parameters and patient-reported outcomes.

To date, 17 patients with SMA and 4 patients with CM have been enrolled. Comprehensive updates on patient recruitment as well as preliminary findings on personalized goal setting and the development of individualized functional strength exercises, will be presented.

P79
Active NBS: A fully remote, multicenter initiative for longitudinal motor monitoring in infants with SMA identified by newborn screening

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The implementation of newborn screening (NBS) for spinal muscular atrophy (SMA) has profoundly altered the natural history of the disease by enabling treatment shortly after diagnosis. However, important questions remain regarding the mid- to long-term motor trajectory of children diagnosed and treated through screening programs, particularly those with two ***SMN2*** copies, who remain at risk for early disease manifestations despite timely intervention. This issue is even more relevant with emerging add-on therapies, for which the optimal timing of initiation is not yet defined. To address these gaps, the Active NBS project was established as a collaborative initiative providing systematic, longitudinal follow-up of infants identified and treated early through NBS or sibling testing. By generating robust, multicenter data, the project seeks to refine our understanding of disease progression under current standards of care and inform when additional or combined therapies may achieve the greatest benefit with the least burden for families, ensuring equal opportunities for children regardless of where they live.

The consortium currently includes the NMRC of Liege (Belgium), coordinating data collection for patients recruited across Europe, the MDUK Neuromuscular Center in Oxford (UK) for the United Kingdom, and the Gemelli Hospital in Rome (Italy) for Italian participants, with additional centers expected or welcomed to join.

Active NBS is an academic, fully decentralized observational study starting from 4 months of age, with all procedures, including informed consent, conducted remotely. Motor development is assessed using two **innovative** digital tools: (1) The MAIJU suit, a sensor-equipped recording infants' positions and movement quality, used until children achieve independent walking (plus a short transition), providing continuous measures such as the BIMS. (2) The Syde® wearable sensors, used in ambulant children to capture real-life gait parameters such as the Stride Velocity 95th Centile (SV95C). This design removes the need for on-site visits, reduces the burden on families, and allows continuous, valid home-based monitoring across countries. Participants are followed up to 30 months, with monthly MAIJU sessions and Syde® assessments every three months.

The primary objectives are to validate digital outcome measures (BIMS and SV95C) in SMA populations and in controls and to characterize early motor trajectories by genotype and treatment status. A data federation model will enable analyses of international cohorts without sharing or transferring data. A real-world dataset strengthens natural history knowledge and supports regulatory qualification of digital biomarkers. This innovative design, combining remote assessments, wearable technology, and federated data analyses, is expected to generate high-quality evidence to guide early intervention strategies and optimize long-term outcomes for children diagnosed with SMA through NBS.

P81

Outcome of newborn screening for Spinal Muscular Atrophy in The Netherlands

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Spinal muscular atrophy (SMA) is caused by homozygous loss of function of the survival motor neuron 1 ***(SMN1)*** gene and characterized by progressive weakness in the course of weeks to years. Its natural history is one of infantile death for cases with early onset (i.e. SMA type 1) and severe disability for chronic forms (type 2 and 3). Early treatment with nusinersen, onasemnogene abeparvovec or risdiplam yields the best outcomes. Newborn screening (NBS) programs for SMA are therefore implemented in a growing number of countries. We here describe the first 50 infants identified through NBS in the Netherlands.

Data were prospectivley collected from June 2022 to September 2025 at the national SMA Center, which provides genetic treatment for all patients in in the Netherlands (population 18 million). NBS uses multiplex qPCR as a first-tier test to detect homozygous ***SMN1*** deletions**.** After referral, a second-tier MLPA test confirms results and determines ***SMN2*** copy number, they key predictor of expected disease severity.

We identified 50 newborns with confirmed homozygous ***SMN1*** deletions via NBS over 38 months, averaging 16 referrals per year (0,0095% of live births). Median referral age was 9 days (IQR 7-10), followed by a visit to the clinic 1 day later (IQR 1-3). Confirmation by MLPA took 3 days (IQR 2-3).

Among 50 newborns, 2 had 1 ***SMN2*** copy, 21 had 2 copies, another 21 had 3 copies and 6 had 4 copies. Four infants were hospitalized prior to NBS due to prenatal onset and severe weakness included two with 1 copy and two with 2 copies. Baseline motor function (CHOP-INTEND, maximum score 64) median scores were 44 (IQR 35-51) in infants with 2 ***SMN2*** copies and 54 (IQR 52-55) in infants with 3 or 4 ***SMN2*** copies. Until April 2024, median treatment initation age was 25 days (IQR 22-31), primarily due to delays in viral gene therapy preparation and delivery. After a new reimbursement policy allowing risdiplam bridging form referral,median age dropped to 10 days (IQR 9-12). Seven infants (14%), two with 1 ***SMN2*** copy and five with 2 ***SMN2*** copies, were untreated due to poor baseline condition. One infant with 2 ***SMN2*** copies died despite treatment with onasemnogene abeparvovec. Two infants discontinued risdiplam due to severe weakness worsening. Overall, 9 out of 50 (18%) infants died, compared to an expected 46% (23/50) based on natural history.

A nationwide newborn screening program for Spinal Muscular Atrophy identified 50 infants in 38 months. Early detection enables prompt treatment, which significantly reduced early mortality and likely improves developmental outcomes. While NBS facilitates early diagnosis and treatment, a substantial proportion of infants with 2 ***SMN2*** copies present mild to severe symptoms of SMA at diagnosis. This is reflected in our data by lower CHOP-INTEND scores in infants with 2 ***SMN2*** copies compared to those with 3 and 4 copies. Long-term follow-up is essential to fully assess early intervention effects.

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Long-Term real-world outcomes following Onasemnogene Abeparvovec Monotherapy for patients with Spinal Muscular Atrophy: Updated findings from the RESTORE Registry

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Onasemnogene abeparvovec (OA), a one-time gene therapy for spinal muscular atrophy (SMA), has been evaluated in several clinical trials and long-term follow-up studies. However, long-term, real-world OA data are limited. RESTORE, a multinational, non-interventional SMA registry, is a successful industry/academia collaboration and robust real-world instrument. Previous RESTORE findings have been reported for OA monotherapy-treated patients (N=168; 13.7 months mean follow-up). Here, we build on long-term safety, effectiveness, and durability evidence for OA monotherapy in a larger RESTORE patient cohort with greater follow-up duration.

Motor function was assessed using the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), Hammersmith Functional Motor Scale – Expanded (HFMSE), and the Hammersmith Infant Neurological Examination – Section 2 (HINE-2).

Of 251 patients (May 23, 2024, data cutoff), median (IQR) ages at SMA diagnosis and OA infusion were 1 (0–6) month and 3 (1–8) months, respectively. Median (IQR) time from OA infusion to last visit was 23.6 (14.3–35.7) (range, 0.5–61.6) months. Patients were diagnosed through newborn screening (n=147, 58.6%) or clinical assessment (n=104, 41.4%). Most had two (n=112, 44.6%) or three (n=106, 42.2%) survival motor neuron 2

(SMN2) gene copies and were treated in the United States (n=173, 68.9%). Of the 61 patients in safety analysis set 1 (patients for whom safety data were available from the time of OA administration), 38 (62.3%) had an adverse event (AE); 24 (39.3%) had related AEs, which were serious in four patients (6.6%). Of 227 patients in safety analysis set 2 (includes all patients with available safety data at any time after OA administration), 109 (48.0%) had an AE; 54 (23.8%) had related AEs, which were serious for seven patients (3.1%). Most common AEs of special interest were hepatotoxicity (n=52, 22.9%), cardiac AEs (n=31, 13.7%), and transient thrombocytopenia (n=28,12.3%). Six deaths (2.4%) occurred. Overall, most patients demonstrated improvements in motor function scores, with 102 of 115 patients assessed (88.7%) achieving or maintaining CHOP INTEND scores of ≥40 points (achieved, n=33 [28.7%]; maintained, n=69 [60.0%]). Mean (SD) months between CHOP INTEND assessments was 12.9 (10.1) months. Similarly, 52 of 55 patients assessed (94.5%) achieved or maintained ≥3-point improvements in HFMSE scores (achieved, n=41 [74.5%]; maintained, n=16 [29.1%]). HINE-2 scores also demonstrated progressive increases over time, with 11 patients achieving the maximal score of 26 (SMN2 copies: two (n=3); three (n=3); ≥4 (n=5). Motor function improvements were maintained for up to 5 years.

These data, while limited to patients treated with OA as monotherapy, indicate therapeutic benefit for up to 5 years post-dosing, providing further evidence for OA as a durable treatment for patients with SMA.

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Motor Function improvement with Nusinersen in SMA: Insights from a functional status–stratified meta-analysis

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Spinal muscular atrophy (SMA) is a rare neuromuscular disorder with progressive weakness. Nusinersen, the first approved disease-modifying therapy, has demonstrated benefit across SMA types. However, functional outcomes stratified by motor ability (walker, sitter, non-sitter) remain insufficiently described.

This systematic review and meta-analysis followed PRISMA 2020 guidelines. Searches were conducted in PubMed, Embase, and Cochrane Central on January 8, 2025. We included observational studies reporting motor outcomes by functional status in genetically confirmed SMA patients treated with nusinersen for ≥12 months. Outcomes were changes in Hammersmith Functional Motor Scale–Expanded (HFMSE), Revised Upper Limb Module (RULM), and 6-Minute Walk Test (6MWT). Mean differences (MD) with 95% confidence intervals (CI) were calculated. Risk of bias was assessed using the MINORS tool.

Fifteen studies comprising 1,168 patients were included. At one year, both sitters and walkers showed significant HFMSE improvement (sitters: MD = 2.70, 95% CI [1.23, 4.17]; walkers: MD = 2.88, 95% CI [1.28, 4.48]). RULM gains were greatest in sitters (MD = 1.06, 95% CI [0.54, 1.58]), while walkers had smaller, non-significant increases. Walkers demonstrated significant 6MWT improvement (MD = 21.55 m, 95% CI [9.68, 33.42]). At two years, HFMSE changes in sitters were modest and non-significant (MD = 1.39, 95% CI [−0.64, 3.41]), suggesting stabilization.

Nusinersen is associated with meaningful functional gains within the first treatment year, particularly among sitters and walkers. Stratification by functional status enhances clinical interpretation and underscores the need for standardized outcome reporting and long-term follow-up in SMA studies.

P87

A dosage study for AAV9-Mediated gene therapy and the development of a CRISPR based combinatorial therapy for the treatment of Spinal Muscular Atrophy

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While current therapies have successfully enhanced SMN production, improved motor function and increased lifespan for most patients with spinal muscular atrophy (SMA), there remains a subset who are refractory to the treatment. Moreover, even for those who respond well, no therapy is curative and for this reason an exploration of novel and co-therapies is warranted. With the occurrence of hepatotoxicity as a common adverse event following the use of adeno associated virus (AAV)-based therapy, a pause and reflection on the potential toxicities that may occur due to supra-physiological levels of SMN or due to high concentrations of AAV used in the gene therapy approach, is necessary. Our lab has shown positive therapeutic effect following the administration of AAV9-cba-SMN in the delta7 mouse model of SMA, however, the minimum dose required to produce an effect remains unknown, as does the duration of the response. Understanding the effect of lower dosage on lifespan and tissue repair as well as the potential for low dose AAV-based therapy to be used in combination with secondary treatment, such as a CRISPR-base editor, could provide benefits in the pursuit of future safe and effective combinatorial therapies.

Currently, our laboratory is evaluating the impact of low doses of AAV9-cba-SMN on the lifespan of delta7 SMA mice, the health of -motor neurons and on subsequent muscle functioning. Firstly, we are conducting a dose escalation study of AAV9-cba-SMN using doses of $0.9x10^{10}$ vg, $1.8x10^{10}$ vg, and $3.7x10^{10}$ vg. Our results demonstrate an increase in survival of delta7 mice from a median of 13 days to a median of 14 days, 22 days and 38 days, respectively with each increasing dose. A dose dependent increase in the rate of weight gain is also observed. In the lumbar spinal cord, we have measured a dose dependent increase in -motor neuron number and cell body size. At the neuromuscular junction, treated delta7 mice show a dose dependent reduction in neurofilament accumulation. Consistent with these findings, a decreased concentration of neurofilament-light chain in plasma was measured. Interestingly, we did not detect any difference in muscle fiber area following treatment at any dose, however, a dose dependent reduction in the number of fibers displaying centralized nuclei is observed. Delta7 SMA mice treated at the highest dose demonstrate a significant reduction in righting time at age P11, with mice treated at the lower doses demonstrating improvement by P13.

Collectively, the information from this dose escalation study has allowed for the development of an AAV9-cba-SMN treatment model. I have selected the dose of $1.8x10^{10}$ vg, to be evaluated in combination with a novel CRISPR-base editing therapy that has shown promise in its ability to edit the ***SMN2*** gene. Future studies will evaluate the potential of this combinatorial therapy and its ability to improve the lifespan, rescue neuromuscular tissues and increase motor ability in delta7 SMA mice.

P89

An update on MAP the SMA: A machine-learning based algorithm to predict THErapeutic response in SMA

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Spinal Muscular Atrophy (SMA) presents significant challenges in predicting therapeutic response due to the heterogeneous nature of disease progression among patients with similar phenotypic characteristics. Accurate prediction of motor outcomes is crucial for optimizing treatment strategies and clinical decision-making.
To develop a predictive machine learning model capable of forecasting therapeutic response in SMA patients by predicting scores from established motor function assessment scales that capture disease progression patterns.
We implemented a two-step model combining mixed-effects models and a latent class model. The former models generate individual predictions on specific motor scales (CHOP INTEND, Hammersmith, RULM, 6-minute walking test) and are integrated with the latent class models, which clusters individual patient trajectories into different groups, thereby uncovering distinct underlying processes that shape common therapeutic responses among patients.
The mixed-effects models analyse data from all SMA types and include fixed effects for patient characteristics including age, SMA type, genetic details, treatment type and motor test scores, and grouped random effects for motor function and SMA type. These models provide two types of forecasts of disease progression: a short-term forecast by using all available information up to the current visit to predict the outcome at the next clinical visit, and a long-term forecasting by iteratively chaining short-term predictions. For each given SMA type, a multivariate latent class model simultaneously describing the time evolution of different motor scores was used to identify different classes of patients sharing similar profiles of trajectories. These models include all the fixed and random effects of the mixed-effects models, but omit historical scores and SMA type. Information metrics were used to identify the optimal number of classes for each SMA type.

The analysis revealed distinct patient subgroups through multivariate latent class modeling. Information metrics identified an optimal three-class model that successfully classified patients into three distinct disease progression profiles. The latent class structure showed clear differentiation in outcome measures progression patterns over time.

MAP the SMA successfully identified clinically meaningful subgroups of SMA patients with distinct therapeutic response patterns. The model's ability to perform both immediate and long-term predictions provides valuable insights for personalized treatment planning and prognosis assessment. The identification of responder classes offers potential for stratified treatment approaches and improved clinical trial design in SMA research. Future validation against Patient-Reported Outcome Measures (PROMs) will further enhance the clinical utility and patient-centered relevance of the predictive
model.

P91

Long-term efficacy and safety of Risdiplam in adults with 5q spinal muscular atrophy (SMA): A large prospective multi-centre observational study

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Risdiplam is an orally administered disease modifying therapy (DMTs) accessible to the adult persons with 5q-associated spinal muscular atrophy (SMA). Real world evidence (RWE) of efficacy of Risdiplam in the adults with SMA is limited by smaller cohorts and shorter duration of follow up. Evidence of the safety and tolerability of Risdiplam in various adult populations have been previously reported in several other cohorts. Risdiplam was accessible to adult SMA patients in the UK since September 2020 via dedicated neuromuscular centres appointed to deliver DMTs to SMA patients, forming a network of centres called Adult SMAREACH UK, where patients are systematically monitored. We investigated the efficacy, safety and tolerability of Risdiplam in adults with 5q SMA over 42 months, the longest time period to date in a large multi-centre cohort of SMA patients. Our primary end point was the change from baseline in motor function measures at 24 months.

Appropriate outcome measures were selected for monitoring depending on the functional status of the SMA patients and which included: Hammersmith Functional Motor Scale Expanded (HFMSE) or its revised version (RHS), Revised Upper Limb Module (RULM), ATEND, EK2 and patient reported outcome measures (PROMs). Data were collected at baseline and 6, 12, 18, 24, 30, 36, 42, and 48 months after treatment initiation. We report baseline characteristics, subgroup analysis and least squares mean (LSM) change from baseline for various motor outcome measures and explored reported adverse events for new safety signals in our large SMA cohort.

Overall, 268 patients who met the inclusion criteria, with a total of 1176 visits, were included in the analysis. The mean age was 35.4 years (SE ±0.31, 15.6-80.8) and 47.8% (n=133) were female. All SMA types were represented in our cohort with Type 2 n=144, (53.7%) and Type 3, n=113 (42.2%) being the commonest. The commonest functional status in our cohort was either sitters or non-sitters (88%) and only 10.8% were ambulant. Baseline motor function (mean values ±SE): RULM 14.9 (SE±0.76), RHS 23.8 (SE± 2.59) and the ATEND score 25.4(SE±0.91), HFMSE 16.6(SE±3.44) and EK2 22.0(SE±0.69). The FVC percentage predicted was 63.5%(SE±3.01). Details of PROM data will be presented at the conference. When considering the overall population of SMA patients on Risdiplam, there were significant increases in several motor outcome measures compared to the baseline, whilst others remained stable over the follow up period of 42 months, after which time point numbers were too limited. Several subgroup analysis and data for change over time in various motor outcome measures will be presented in detail along with PROMs data. There was no new safety signals identified.

Our prospective, observational, long-term (42 months) data provide substantial real-world evidence, that describes the efficacy and safety of Risdiplam in a large cohort of adult patients with SMA from the UK.

P93
RAINBOWFISH: 3-year efficacy and safety data of risdiplam in children with presymptomatic SMA

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Risdiplam (EVRYSDI®) is a centrally and peripherally distributed, oral survival of motor neuron 2 (SMN2) pre-mRNA splicing modifier approved for the treatment of spinal muscular atrophy (SMA).
RAINBOWFISH (NCT03779334) is a global, open-label, single-arm, multicentre, Phase 2 study assessing the efficacy, safety and pharmacokinetics/pharmacodynamics of risdiplam in children with genetically diagnosed and presymptomatic SMA from birth to 6 weeks of age (at first dose), regardless of SMN2 copy number.
RAINBOWFISH enrolled 26 children who had two (n=8), three (n=13) or ≥4 SMN2 copies (n=5). The primary efficacy (PE) population (n=5) had two SMN2 copies and baseline compound muscle action potential (CMAP) amplitudes ≥1.5mV. Drug dosage was adjusted to achieve a target exposure of approximately 2,000 ng·h/mL.
The primary endpoint was met after 1 year of risdiplam treatment, with 4/5 (80%) children in the PE population able to sit without support for ≥5 seconds (Item 22 of the of the Bayley Scales of Infant and Toddler Development, third edition [BSID-III] gross motor subscale).
Twenty-three children completed 2 years of treatment with risdiplam (data cut-off: 27 March 2024). All children with 2 SMN2 copies who reached Year 2 could sit without support, and most were able to stand and walk (assessed by Items 40 and 42 of the BSID-III gross motor subscale and Hammersmith Infant Neurological Examination, Module 2). All children with ≥3 SMN2 copies achieved standing and walking, and most achieved these milestones within the World Health Organisation windows of typical child development.
All children were able to swallow and feed orally, and none required respiratory or nutritional support. Mean scaled scores from the BSID-III cognitive scale were consistent with skill development typical of children their age. Over two years, no treatment-related adverse events led to withdrawal or treatment discontinuation.
Here we report, the 3-year efficacy and safety data from RAINBOWFISH.

P94
Delphi-Based Guidelines for Orthopedic and Physiotherapeutic Management of Scoliosis in Children with Spinal Muscular Atrophy

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Scoliosis is a common and often progressive complication in children with Spinal Muscular Atrophy (SMA), significantly impacting their posture, function, and respiratory capacity. Optimal management requires close collaboration between orthopedic surgeons and physiotherapists. This abstract presents the outcomes of a Delphi study aimed at establishing evidence-informed guidelines for the orthopedic and physiotherapeutic care of scoliosis in the pediatric SMA population.

A multidisciplinary panel of experts, including pediatric orthopedists specializing in neuromuscular scoliosis and experienced physiotherapists working with children with SMA from Poland and other countries, participated in a multi-round Delphi process. The study aimed to achieve consensus on key aspects of scoliosis management, including screening and monitoring protocols, indications and timing for conservative treatments (e.g., bracing, specific physiotherapy), and criteria for surgical intervention.

The Delphi process explored various aspects of assessment, such as the frequency and methods of radiographic evaluation, clinical assessment techniques specific to SMA-related scoliosis, and the role of respiratory function in decision-making. Regarding conservative management, the study focused on specific physiotherapy interventions (e.g., respiratory exercises, postural training, active-assisted movements) that demonstrate the greatest benefit in this population. Furthermore, the guidelines address the indications for different surgical approaches, the timing of surgery in relation to disease progression and functional status, and post-operative rehabilitation strategies.

The resulting Delphi-based guidelines provide a framework for orthopedic surgeons and
physiotherapists to standardize and optimize their approach to scoliosis in children with SMA. These guidelines emphasize the importance of early identification, individualized treatment plans considering the child's specific SMA type and functional abilities, and ongoing interdisciplinary communication. The implementation of these guidelines has the potential to improve clinical outcomes, enhance the quality of life, and reduce the incidence of medical emergencies associated with severe scoliosis in children with SMA

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SMA Care UK: Optimising bone health for individuals with SMA across the UK

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The 2018 international care recommendations for spinal muscular atrophy (SMA) were published prior to the availability of disease-modifying treatments (DMTs), which have significantly altered the clinical course, phenotype and prognosis of the condition. These guidelines, intended as a global minimum standard of care, were largely focused on paediatric populations and did not account for the novel and evolving phenotypes now observed. Furthermore, whilst they established a foundation for musculoskeletal management in SMA, bone health was not a primary focus.

SMA Care UK is a collaborative initiative involving healthcare professionals, people living with SMA and other stakeholders. Its goal is to update evidence-based standards of care and harmonise best practice in response to the priorities of the SMA community and the changing landscape of SMA.

Increasing evidence demonstrates that individuals with SMA are at heightened risk of reduced bone mineral density, osteoporosis and fragility fractures, attributable to immobility, muscle weakness, nutritional factors and altered bone metabolism. In the context of DMTs, which have extended survival and broadened phenotypic expression, bone health has emerged as a critical component of long-term care. These developments highlight the need for dedicated clinical guidance to support systematic assessment, monitoring and management of bone health across the paediatric-to-adult spectrum.

In response, a multidisciplinary team of individuals living with SMA, expert adult and paediatric healthcare professionals, including adult and paediatric Neurologists, Endocrinologists, Rheumatologists and a Clinical Scientist, has undertaken a comprehensive review of the current evidence and practice for bone health management in SMA. Drawing on emerging data, evolving clinical experience and identified areas of unmet need, the group will develop guidance covering assessment, monitoring and therapeutic interventions. The group is working with relevant professional bodies and NICE, so that guidance can be endorsed and published once consensus is achieved.

In parallel, gaps in evidence are being highlighted and strategies will be developed to address these, including future evidence-gathering and collaboration with international networks to ensure that updated guidance remains aligned with global best practice.

*These authors jointly lead SMA Care UK.

P98
SMA Care UK: A national initiative to ensure that those living with SMA receive the best possible care

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*These authors jointly lead SMA Care UK

Spinal muscular atrophy (SMA) is a genetic disorder causing progressive muscle atrophy and weakness. International Standard of Care were published in 2018 prior to the approval of the currently available disease-modifying treatments (DMTs). These guidelines were intended as a global minimum standard of care for people with SMA regardless of their country of residence. The introduction of DMTs has altered the course of the natural history and created evolving phenotypes. This change and the fact that the previous standards of care were largely focused on paediatric populations, has triggered the need to update and adapt the provided guidelines to the current scenario in the UK.

SMA Care UK is a collaborative initiative involving healthcare professionals, people living with SMA, caregivers and other stakeholders, established to update and support the implementation of evidence-based standards of care across the UK. Its goal is to address current priorities and harmonise best practices in response to the changing landscape of SMA management and support their implementation across the UK.

One of the topics deemed to be a priority was the development of spinal management guidelines that provide an updated approach to both conservative and surgical interventions.

In response, a multidisciplinary team of expert paediatric and adult healthcare professionals, including physiotherapists, neurologists, spinal surgeons and orthotists, undertook a comprehensive review of the current recommendations for spinal care in people with SMA. Drawing on emerging evidence, evolving clinical practice and areas of unmet need, they identified areas requiring revision alongside with evidence gaps. This process led to the development of 37 statements covering the assessment, management and treatment of spinal complications in people with SMA, stratified according to functional status and spanning the paediatric-to-adult continuum. The lived experience of people with SMA was sought prior to running a Delphi study to build consensus within the SMA REACH network. Endorsement of the resulting guidance will be sought from key stakeholders.

In parallel, future research questions were suggested based on the highlighted key gaps in evidence.

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SMA Care UK: Ensuring the best management of spine for individuals with SMA across the UK

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In parallel, future research questions were suggested based on the highlighted key gaps in evidence.

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Minimally invasive fusionless surgery for Scoliosis in Spinal Muscular Atrophy

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Innovative, targeted therapies for spinal muscular atrophy (SMA) are improving prognosis and survival rates, particularly in severe cases. Although motor function has shown improvement in both clinical trials and real-world studies, scoliosis remains a major complication from an early age. Spinal fusion is the preferred surgical option for SMA scoliosis but requires skeletal maturity, making it unsuitable before puberty. In younger children, conservative treatment has been the mainstay for managing axial collapse, demonstrating effectiveness during the early years, although its benefits become less consistent during growth spurts. Over the past decades, several fusionless techniques have been proposed for early scoliosis treatment.

In this study, we report the clinical, radiologic, and respiratory outcomes of minimally invasive fusionless surgery (MIFLS) in nine patients with SMA. The series included five patients with type 2, three with type 3, and one with type 1. All but one were non-ambulant at the time of surgery. All but one patient had initiated nocturnal noninvasive ventilation (NNIV) before surgery, and two patients received enteral nutrition via gastrostomy tube (GT) to optimize body weight. All patients were receiving nusinersen or GT before surgery and were transitioned to risdiplam at the time of surgery.
The mean age at surgery was 9.3 years (range 6.9–12.6 years), with a mean follow-up of 1.8 years (range 1 month–4 years). The mean major coronal curve improved from 70 ± 11° to 22 ± 16°, thoracic kyphosis decreased from 54 ± 9° to 33 ± 10°, and pelvic obliquity decreased from 26 ± 6° to 3 ± 2°. No mechanical or infectious complications were observed, and no patient required rod lengthening procedures. Respiratory function remained stable, with no significant postoperative decline.
In conclusion, bipolar MIFLS in SMA patients preserves spinal and thoracic growth without interfering with respiratory function. It provides a significant and sustained correction of scoliosis, kyphosis, and pelvic obliquity, with a low rate of complications. In patients with implanted spinal instrumentation, risdiplam has facilitated continuous therapeutic management

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When treatment stops or never starts: Characteristics and experiences of people living with SMA in Europe

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Spinal muscular atrophy (SMA) is a progressive, degenerative neuromuscular condition characterised by difficulties in movement and in reaching or maintaining motor milestones such as sitting and walking. Morbidities across multiple domains are common, including bulbar, respiratory, musculoskeletal and metabolic function. Since 2017, three disease-modifying therapies (DMTs) have become accessible to varying degrees across global markets. Both clinical trial and real-world data show that these therapies have changed the trajectory of SMA by slowing or stabilising disease progression and, in some cases, restoring lost function. Consequently, DMT treatment is now considered standard of care. Nevertheless, a proportion of individuals living with SMA either never initiate or discontinue treatment. The aim of this study is to systematically examine the reasons for either not starting or discontinuing treatment, as well as the characteristics and experiences of this patient population.

We analysed data from SMA Europe's 2025 community survey (n=826) and selected respondents from geographical Europe (n=588). In this latter group, 78 respondents (13.5%) reported never having received a DMT, either because they did not want treatment (n=16) or lacked reimbursement (n=55). Reported reasons for lack of reimbursement included respiratory support (n=4), not meeting clinical or genetic requirements (n=4), not meeting performance requirements (n=9), not meeting age criteria (n=14), and other reasons (n=15, mostly related to cost).
In addition, 93 respondents (20.2%) reported that their treatment had been discontinued. The most frequently reported reasons included perceived inefficacy by the patient/caregiver (n=23) , a worsening of symptoms that forced to stop treatment, no longer meeting reimbursement criteria due to changes in clinical status (n=9), side effects (n=19), new reimbursement restrictions (n=3), waiting for reimbursement renewal (n=5), supply shortages or delivery delays (n=18), the ending of an expanded access programme (n=3), burden of administration (n=3), lifestyle interference (n=10), pregnancy (n=4), and other (n=34). Among these, treatment was discontinued for less than a month in 14 cases, for one to three months in 14 cases, and for more than three months in 59 cases. The most commonly reported symptoms after stopping treatment included decreases in mobility (n=24, 28.2%), in muscle strength (n=34, 40%) and in endurance (n=33, 38.8%), and increased fatigue (n=30, 35.3%).

These findings demonstrate that a substantial proportion of the European SMA population faces barriers to accessing or continuing treatment due to medical, regulatory or logistical factors. Addressing these challenges requires collective action from all stakeholders to ensure equitable and continued access to DMTs, so that all individuals living with SMA can benefit from recent scientific advances regardless of geography, demographics or clinical characteristics.

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Consensus statement on management of hip displacement in Spinal muscular atrophy in the disease modifying therapies era

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Spinal muscular atrophy (SMA) is a genetic neuromuscular disorder caused by bi-allelic deletions or pathogenic variants in the ***SMN1*** gene, with SMA Type 1 being the most severe form with early muscle weakness, failure to achieve motor milestones, and limited survival. Disease-modifying therapies (nusinersen, risdiplam, and onasemnogene abeparvovec) have improved survival and motor outcomes but have also created new challenges, including orthopaedic care. Management of hip displacement in SMA remains controversial, with approaches ranging from conservative to surgical. A Delphi consensus exercise was conducted in the United Kingdom (UK) to provide national guidance.

The process included two rounds involving 45 senior health care professionals (neurologists, orthopaedic surgeons, physiotherapists and patient's representative) from 19 British leading paediatric neuromuscular centres. Online Round 1 included 16 statements, resulting in consensus (>75% agreement) on six statements. Combined online and in-person Round 2, allowed for live voting, modification and final approval of further seven statements. Family input gathered by advocacy representatives also informed the discussions.

The final consensus includes 13 approved statements addressing key aspects of hip and contractures management in SMA. The recommendations emphasize individualized, multidisciplinary assessments and proactive strategies to prevent hip dislocation, particularly in children with higher motor potential, while acknowledging the lack of current evidence and the need to collect long-term data. Key recommendations included timeline for radiographic hip surveillance, and orthopaedic approach to painful hips as well as muscle and joint contractures. The consensus highlights the importance of building national database (SMA Reach UK registry) and developing evidence-based guidelines for both conservative and surgical approaches. The potential role of less invasive approaches was discussed as an option for selected cases.

This study emphasizes the importance of multidisciplinary collaboration and individualized care in optimizing orthopaedic management for SMA patients. By addressing gaps in clinical practice, the consensus recommendations provide a foundation for consistent, evidence-based care while promoting research and audit initiatives. This is the current evidence and clinical expertise based National Guidance for the UK and the first of its kind internationally.

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Longitudinal course of joint range of motion in children with spinal muscular atrophy receiving disease-modifying agents

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In treatment-naïve spinal muscular atrophy (SMA), a progressive decrease in joint range of motion is a well-recognized disease characteristic. However, it remains unclear how this trajectory evolves in children receiving disease-modifying treatment (DMT).

To prospectively examine the longitudinal course of joint range of motion in young children with SMA treated with disease-modifying agents.

We included children with SMA (with 2 or 3 *SMN*2 copies) who started treatment within the first 18 months of life in a prospective national tertiary cohort study. Our examination consisted of joint range of motion of the knee, elbow and wrist; the longitudinal course was studied using linear mixed-effects models.

We analysed 165 visits of 39 children (median age 22 months; interquartile range [6-45]) with treated SMA over a 3-year follow-up period. The median age at start of treatment was 2 months [range 0-8]. We found an average yearly decline in knee extension mobility of 3˚. The overall course of range of motion for elbow and wrist remained stable.

The course of joint mobility in early-treated children with SMA is characterised by a decline in knee extension and a stable range of motion of wrist and elbow joints. We stress the importance of monitoring knee range of motion at least every six months and adopting a proactive approach to maintain full knee extension for lifelong mobility.

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292nd ENMC workshop: Best practices after positive Spinal Muscular Atrophy newborn screening

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The 292nd ENMC workshop was held from 23–25 January 2026 in Hoofddorp, The Netherlands, and brought together neuromuscular experts and patient representatives from Europe, North America, and Australia to discuss best practices following a positive newborn screening (NBS) result for spinal muscular atrophy (SMA). The meeting addressed key post-screening steps, including confirmation of the diagnosis, communication with families, treatment decision-making, timelines to treatment, and long-term follow-up.

SMA is a rare neuromuscular disease caused by the absence of the SMN1 gene, leading to progressive motor neuron degeneration. Therefore, weakness of voluntary muscles mainly dominates the manifestations with a variable degree of involvement, ranging from very severe congenital cases to weakness that may appear in adult life. While SMN1, the determinant gene, is missing, SMN2 acts as a backup gene, producing small amounts of functional SMN protein. Thus, the number of SMN2 gene copies influences, without fully predicting, disease severity. The more SMN2 copies, the less severe the manifestations. The availability of disease-modifying therapies and evidence showing that treatment is most effective when started early have motivated the rapid expansion of NBS programmes worldwide. However, early identification also introduces challenges: variability in SMN2 copy number assessment, uncertainty in prognosis (particularly for infants with ≥4 SMN2 copies), the emotional burden on families receiving an unexpected diagnosis, and the shared decision-making in therapy choice with management of expectations.

The workshop aimed to harmonise approaches for confirming the genetic diagnosis, particularly regarding the determination and quality assessment of SMN2 copy number. Another key objective was to define shared principles to guide treatment decisions for both symptomatic and presymptomatic infants detected by NBS, including those with ≥4 SMN2 copies. Participants also sought to identify practical ways to reduce delays between a positive screening result, diagnostic confirmation, and the start of treatment. Communication with families, long-term follow-up priorities, and international data collaboration were key discussion points.
Participants agreed on key laboratory and clinical principles to be integrated into updated best-practice guidelines. These include the need for accurate and repeatable SMN2 copy number testing, harmonised reporting, and re-testing strategies when results are uncertain. For clinical management, participants emphasised that symptomatic infants require immediate treatment without delay by confirmatory testing, and that prolonged "watch-and-wait" approaches for infants with 4 SMN2 copies are associated with poorer outcomes and should be avoided.

The workshop highlighted the importance of standardised pathways to shorten time to treatment, clear communication skills and tools for families, and support measures aligned with each centre's resources. Proposed deliverables include updated

laboratory guidelines, communication recommendations, and development of a minimal international dataset for long-term follow-up and federated data sharing.
The role of multidisciplinary teams in consistent follow-up was underlined. Participants also noted the expanding role of biomarkers, such as neurofilament levels and digital biomarkers, which may support earlier identification of disease activity and help refine prognosis and treatment response.

These outputs will feed into the ENMC workshop report, together with collaborative initiatives aimed at improving real-world data collection.
By promoting earlier and more accurate diagnosis, clearer communication, and timely treatment initiation, the workshop's recommendations aim to reduce disease progression, improve developmental outcomes, and lessen the emotional burden on families. Harmonised standards can also reduce inequalities in access to optimal care across countries.

Next steps include drafting the full workshop report, updating the international NBS white paper (under the umbrella of the European Alliance for Neonatal Screening), defining an international minimal dataset, advancing registry harmonisation efforts, and developing communication guidelines for families.

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SMN transcript variants in SMA: Blood-based dynamics during treatment

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While SMN-restorative treatments have reshaped the clinical management of spinal muscular atrophy (SMA), individual response to therapy is highly variable. This highlights the need for objective biomarkers to monitor treatment efficacy, explain response heterogeneity and ultimately personalise treatment strategies. Since the severity of SMA and the mechanism of current therapies are driven by ***SMN2*** exon-7 splicing, ***SMN2*** transcript variants, including total SMN, SMND7 and full-length SMN (SMN-FL), as well as the SMN-FL/SMND7 ratio, represent plausible blood-based biomarkers.

We quantified SMN transcript variants in the peripheral blood of 50 adults with SMA using RT-qPCR. Baseline expression was related to SMA type, ambulatory status, motor function and respiratory function. Longitudinal trajectories were analysed during treatment with nusinersen (baseline, 24 months) and risdiplam (baseline, 6 and 12 months) to assess treatment-related dynamics of expression.

At baseline, patients with four ***SMN2*** copies had higher levels of total SMN, SMND7, and SMN2-FL than patients with three ***SMN2*** copies. The levels of all three transcripts were also higher in ambulant compared to non-ambulant patients, and the differences remained significant after adjustment for age, disease duration, and ***SMN2*** copy number. All three SMN transcripts also correlated positively with motor and respiratory function, with most associations remaining significant after adjustment. In contrast, the SMN-FL/SMND7 ratio did not differ significantly by ***SMN2*** copy number or ambulatory status and showed no association with motor or respiratory function. Under nusinersen treatment, total SMN showed a small but significant reduction at 24 months, and SMND7 exhibited a decrease close to significance. By contrast, risdiplam treatment resulted in a splicing shift: SMN-FL increased significantly at 6 and 12 months, SMND7 decreased significantly at 6 months, and the SMN-FL/SMND7 ratio increased at 6 months and trended towards significance at 12 months.

Our results suggest that SMN transcripts could serve as valuable blood-based biomarkers for the assessment of SMA disease severity and treatment response. However, further studies are needed to validate these biomarkers and investigate their utility for personalising treatment strategies for SMA patients.

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MyomiRNA networks in SMA: Exploring biomarker candidates of disease severity and treatment response

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SMN-restorative therapies have significantly impacted the clinical course of spinal muscular atrophy (SMA), yet an unmet need remains for robust, quantitative molecular biomarkers to effectively monitor disease progression and treatment response. Circulating RNAs represent promising candidates, as they reflect key pathological processes in SMA, including motor neuron integrity, neuromuscular junction function, and muscle maintenance. To elucidate disease mechanisms and identify potential biomarkers, our study analysed the expression of four SMA-associated miRNAs, ten predicted mRNA targets, and two interacting lncRNAs in the peripheral blood of SMA patients.

The selected RNAs from 50 adult SMA patients were quantified by RT-qPCR. Pre-treatment expression levels were analysed in relation to SMA type, ambulatory status, motor function, and respiratory function. Longitudinal changes were analysed during treatment with nusinersen (baseline, 24 months) and risdiplam (baseline, 6 and 12 months) to assess expression dynamics during treatment.

At baseline, miR-206 expression was significantly higher in SMA type III than type II and in ambulatory versus non-ambulatory patients, while miR-1-3p was significantly lower in type III than type II patients. After adjustment for SMN2 copy number, these type-based differences were no longer significant. miR-206 correlated positively with motor and respiratory function, while miR-133a-3p and miR-133b correlated negatively with respiratory function, and these associations remained significant after adjustment for age, disease duration, and SMN2 copy number. Modest age-related differences in expression were observed for PGD, G6PD, and FGFR1, while sex-specific differences were observed for miR-133a-3p, FGFR1, ANXA2, and LINCMD1. Longitudinally, levels of miR-206, LINCMD1, and lnc-GJA1-2 decreased significantly during nusinersen treatment at 24 months, alongside a modest reduction in several targets (PGD, G6PD, TKT, HDAC4, SP1, TGFB1, KCNQ1, IGF1R). In contrast, risdiplam treatment resulted in a decrease in miR-133a-3p levels at 6 months, with no consistent changes in other miRNAs, mRNAs, or lncRNAs at 6 or 12 months.

Our findings on regulatory miRNA-lncRNA-mRNA networks advance the understanding of SMA pathogenesis and reveal novel biomarker candidates for disease severity assessment and treatment monitoring.

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A translation-based biomarker panel to predict disease progression and treatment response in spinal muscular atrophy

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The approval of three SMN-enhancing therapies represents a significant step forward for the SMA community. However, variability in treatment response has also become evident, and a significant portion of this variation remains unexplained. This highlights the need to develop reliable biomarkers to predict disease progression and therapeutic response. Here, we present an innovative approach exploiting the role of SMN in the regulation of mRNA translation. Polysome profiling followed by RNA-seq (POL-seq) identified extensive translational defects in primary patient-derived fibroblasts. These defects were largely rescued by ***in vitro*** risdiplam treatment, which restored 65% of dysregulated transcripts to normal levels. Gene ontology analysis identified ribosome-, translation-, and neuronal-related pathways as the most affected. A panel of 12 proteins from our analyses could be used to successfully cluster samples based on treatment or genotype. Next, a subset of these targets was analyzed in detail in multiple tissues and various time points in the Taiwanese mouse model of SMA mice to assess expression dynamics and response to risdiplam treatment ***in vivo***, showing that expression profiles of these targets could be used to predict disease status and treatment effect. Finally, using an extended cohort of patient-derived fibroblasts with three ***SMN2*** copies we further characterized these targets in a heterogeneous patient context and found that four targets were especially promising to predict varying aspects of SMA and treatment outcomes. We will perform further analyses to determine the suitability for each of these proteins as biomarkers to predict disease and treatment outcomes in patient-derived serum and CSF samples.

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Muscle fiber conduction velocity of the upper arm during low- and high-intensity contractions is lower in patients with SMA than in healthy controls

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Muscle weakness and fatigability are both clinical manifestations of SMA that lead to significant impairment of daily life activities. Muscle abnormalities in SMA typically include slow-twitch (ST) low-force myofiber predominance that contributes to muscle weakness. In healthy individuals, ST myofibers dominate during low-intensity contractions (e.g., 20% of the maximal voluntary contraction (MVC)), whereas at higher intensities (e.g., 60% MVC) fast-twitch (FT) myofibers are additionally recruited. We hypothesize that, due to the reduced pool of FT myofibers with their relatively higher conduction velocities, SMA patients may exhibit lower muscle fiber conduction velocities at high-intensity tasks compared to healthy controls.

In this study, patients with SMA and age- and sex-matched healthy controls performed isometric elbow flexion at a 90˚ elbow joint angle of the dominant biceps brachii during MVC, 20% MVC (120 s), and at 60% MVC until task failure or a maximum of 120 s. Outcome measures included MVC force measured with an isokinetic dynamometer (Biodex System 4), endurance time, median frequency of the power spectrum (MDF) and muscle fiber conduction velocity (MFCV) measured with high-density electromyography (HD-EMG) (Quattrocento, OT Bioelettronica).

Data from 5 patients with SMA (mean age 21.8 ± 7.0 years) and 5 matched controls (mean age 21.6 ± 6.4 years) showed reduced MVC force in SMA (12.1 ± 11.5 Nm) compared to controls (43.5 ± 9.7 Nm). Endurance times were similar between groups (all completed 20% MVC; for 60% MVC, SMA: 73.7 ± 56.9 s and control: 72.2 ± 52.6 s). **MFCV** at the start of the tests was lower in SMA patients at both 20% (4.41 ± 2.83 m/s) and 60% (4.54 ± 1.66 m/s) compared with controls (5.32 ± 0.20 and 5.96 ± 0.50 m/s, respectively). Both MDF and MFCV showed a (non-significant) higher negative slope during the 60% MVC test compared to the 20% MVC test, indicating higher fatigue.

These findings support the hypothesis that in patients with SMA the fiber type composition and motor unit recruitment differ from those in healthy individuals during isometric endurance tests at low and high intensities. Ongoing data collection (target n=20) will allow for more robust statistical analyses, which we will present during the conference. Furthermore, motor unit decomposition, e.g. estimation of recruitment thresholds, can give further insights into recruitment strategies. Understanding SMA-specific motor unit recruitment mechanisms may inform the design of tailored interventions aimed at enhancing type FT myofiber engagement and may contribute to the optimization of outcome measures in therapeutic trials.

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Methylation profile as new biomarkers approach for SMA

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Spinal muscular atrophy (SMA) is a genetic neuromuscular disorder caused by reduced survival motor neuron (SMN) protein, leading to motor neuron degeneration. Early diagnosis and reliable biomarkers are crucial for disease monitoring and personalized treatment. DNA methylation analysis has highlighted an epigenetic alteration in SMA, suggesting its involvement in the disease pathophysiology.

In this prospective study, DNA methylation profiles were analyzed in samples from SMA patients and healthy controls. Genome-wide DNA methylation profiling was performed using the Illumina NextSeq 550 platform. Bisulfite-converted DNA was amplified using the Infinium MethylationEPIC v2.0 kit. Bioinformatic analyses included quality control, data normalization, and differential methylation analysis, with statistical significance adjusted using the Benjamini–Hochberg correction.

DNA methylation analysis of 37 blood samples (31 SMA patients and 6 controls) identified 18 differentially methylated genes and revealed an association between epigenetic changes, SMA severity, and Rab/Rho GTPase signaling pathways. Specifically, the analysis showed genes differentially methylated in SMA patients compared to controls: CHML, ZNRD1ASP/ZNRD1-AS1, LRRC27, MAFK, CACNA1C, DYNC1H1, KIAA1217, HSD11B1L, COL11A2, PPP1R13L, KIF26B, NCOR2, SCRN1, KCNQ1, BRD2, TRIM26, DIP2C and WWTR1, involved in synaptogenesis, neuronal development, calcium signaling, epigenetic regulation and regulation of cell metabolism and proliferation. Additional genes were: SLC, ARHGA, CDK2AP, FBXL, CACNA2, GLT8, involved in protein processing, ion and nutrient homeostasis, neuronal signaling.

This preliminary study identifies distinct DNA methylation signatures in SMA patients, suggesting a relevant role of epigenetic dysregulation in disease mechanisms and biomarker discovery. Further studies are required to elucidate their functional impact.

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A multi-omic and organoid-based platform for Spinal Muscular Atrophy biomarker discovery

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The development of groundbreaking Survival Motor Neuron (SMN) replacement strategies has revolutionized the field of Spinal Muscular Atrophy (SMA) research. However, the limitations of these therapies, influenced by SMN2 copy number, age at treatment initiation, and baseline disease severity, have now become evident, highlighting the need for the development of robust and rapidly detectable biomarkers to guide and monitor treatment. Therefore, in this study, we aim to identify biological markers to support the development of personalized therapies, using human patient-specific 3D organoids. We generated and phenotypically assessed human spinal cord organoids (SCOs) derived from SMA type I and control induced pluripotent stem cells (iPSCs). SCOs were treated with the three currently approved therapies (AAV encoding SMN1 cDNA (onasemnogene abeparvovec-like), a small molecule (risdiplam-like), and an antisense oligonucleotide (nusinersen-like)) aimed at restoring SMN protein levels. Significant cellular and molecular developmental changes across various cell populations, extending beyond motor neurons, were observed in SMA SCOs compared to control SCOs. Notably, SMN-restoring therapies seemed to reverse pathological markers in the SMA organoids. Multi-omic profiling and longitudinal monitoring of soluble biomarkers were performed on SMA 3D organoids to identify specific biomarkers. Overall, SMA-derived organoids offer a platform to identify biomarkers whose integration with clinical and genetic data will enable early phenotypic diagnosis and personalized therapy to ensure better patient outcomes.

P126 - FLASH TALK

Exploring the trajectory of swallowing within psychomotor development in Spinal Muscular Atrophy: Moving toward integrated care

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Spinal Muscular Atrophy type 1 (SMA type 1) is a genetic neuromuscular disease that typically presents before 6 months of age and is characterized by profound hypotonia, progressive muscle weakness, and early involvement of respiratory and bulbar musculature. Swallowing impairment (dysphagia) is a hallmark of SMA type 1 and significantly contributes to morbidity. Despite the documented benefits of disease-modifying therapies (DMTs) in terms of enhanced survival and motor outcomes, their impact on swallowing remains understudied.

This study aims to longitudinally characterize swallowing function in children with SMA type 1 treated with DMTs, while contextualizing these findings in relation to the patients' current motor abilities and cognitive performance.

A single-center, longitudinal, observational study was conducted at Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, from 2021 to 2025. Swallowing function was evaluated using four validated scales (MAS, OrSAT, FILS, and p-FOIS), while motor and cognitive functions were assessed using CHOP-INTEND and age-appropriate cognitive tests. Patients were stratified by baseline swallowing status, pharmacological therapy, and age at DMT administration. Non-parametric statistical tests were applied.
This longitudinal study evaluated swallowing, motor, and cognitive function in 41 children with SMA type 1. No significant changes in swallowing function were observed over one year in the overall cohort or its subgroups, despite significant improvements in motor function. All swallowing scales, except swallowing safety, showed moderate but significant associations with motor and cognitive scores.

In children with SMA type 1 receiving treatment, swallowing function remained largely stable, whereas motor function significantly improved over one year. Baseline swallowing status, type of DMT, and age at administration did not influence the trajectory of swallowing over time. These findings highlight the importance of standardized, longitudinal, and integrated assessments of swallowing, motor, and cognitive functions in the management of SMA type 1.

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Restoration of the B-Raf neurotrophic signaling hub ameliorates neurodegeneration in a mouse model for Spinal Muscular Atrophy

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B-Raf has emerged as a central hub in neurotrophic signaling, playing a critical role in the survival of motor neurons and dorsal root ganglia (DRG) neurons. We have previously shown reduced B-Raf expression together with reduced expression of its interaction partner 14-3-3 in spinal muscular atrophy (SMA), a neurodegenerative genetic disorder affecting motor neurons and DRG neurons.

In this study, we investigated whether B-Raf exerts neuroprotective effects in the $Smn^{2B/-}$ mouse model of SMA. Neonatal mice were cryoanesthetized at post-natal day one and intrathecally injected with various AAV2/1 constructs designed to neuron-intrinsically overexpress either B-Raf alone or B-Raf in combination with 14-3-3 . We assessed vector biodistribution and histopathology.

Both treatment groups exhibited beneficial effects at the histopathological level with no obvious sign of toxicity of the viral constructs. Partial recovery was observed in the neuromuscular junction and muscle fiber size of the tibialis anterior muscle. Notably, co-expression with 14-3-3 fully restored the reduced muscle fiber size seen in $Smn^{2B/-}$ mice.

These findings suggest that reduced neuronal B-Raf/14-3-3 expression contributes to motor neuron pathology in SMA. Moreover, viral restoration of the B-Raf signaling hub downstream of the SMN protein may serve as a treatment regimen when combined with disease-modifying, SMN-enhancing treatments which are currently on the market and which do not fully restore motor neuron health and motor function in all patients with SMA.

P130

Interaction of spinal microglia and astrocytes in late-onset Spinal Muscular Atrophy

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Spinal Muscular Atrophy (SMA) is a hereditary neurodegenerative disorder characterized by loss of motor neurons due to a lack of functional survival of motor neuron (SMN) protein. Patients affected by late-onset SMA subforms often do not benefit from existing therapies making research on further pathomechanisms and therapeutic strategies essential. SMN is ubiquitously expressed in all cells, possibly affecting glial cells, too. It has been shown that glutamate homeostasis of astrocytes is disturbed leading to a glutamate toxicity mediated motor neuron loss. Furthermore, astrocytes can exhibit a neurotoxic phenotype that has already been described in other neuromuscular diseases. Neurotoxic astrocytes can contribute to neuronal loss and aggravate disease progression. Astrocyte neurotoxicity is facilitated by interactions with microglia via upregulation of complement protein C3 in astrocytes. Identifying a similar pathomechanism in late-onset SMA would reveal new therapeutic targets to treat patients not responding to current therapies.

A late-onset SMA mouse model resembling many features of late-onset SMA is used to study astrocyte/microglia interaction in tissue stainings of lumbal spinal cord and tissue and cell cultures. To assess morphology changes of glial cells skeleton and fractal analysis is used to reconstruct cell shape. Immunohistostaining showed a change in microglia reactivity before astrogliosis at P20 in SMA mice. Microglia expressed more Iba-1, were increased in numbers and changed in morphology. Astrocytes were increasingly C3-positive at P28 and exhibited morphology changes, too. Together, this preliminary data suggests a microgliosis before astrogliosis in spinal cord of late-onset SMA mice. Microglia are seemingly capable of influencing astrocyte neurotoxicity, revealing a novel pathomechanism in late-onset SMA and creating possible new therapeutic targets.

P132

Targeting mitochondrial dysfunction in late-onset SMA mice: Metformin as potential therapeutic drug

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Spinal muscular atrophy (SMA) is a neuromuscular disorder caused by a deficiency of functional survival motor neuron (SMN) protein, leading to progressive motor neuron (MN) loss and muscle weakness. While current SMN-enhancing therapies are effective for early intervention, their efficacy in late-onset SMA is limited, highlighting the need of approaches addressing secondary disease mechanisms.

Proteomics of spinal cord tissues was conducted in a mild Taiwanese, also referred as late-onset SMA mouse model, to characterize disease-associated changes. Later, gene enrichment analysis, protein-protein interaction network construction, and an ***in silico*** drug repurposing strategy was proposed. Experimental validation involved, reactive oxygen species (ROS) measurements, mitochondrial complex I activity assays, metformin treatment, and motor behavioral testing to assess therapeutic effects.

Proteomic profiling revealed significant mitochondrial dysfunction in late-onset SMA, including upregulation of respiratory chain complex I proteins and increased oxidative stress. Elevated mitochondrial and cytoplasmic ROS levels were detected in SMA mice spinal cords, correlating with progressive MN loss. Metformin, identified through an ***in silico*** drug repurposing analysis, effectively inhibited complex I activity, reducing oxidative stress and slowing down MN loss. Metformin-treated SMA mice exhibited improved motor behavior, reduced fatigability, and increased nerve conduction velocity compared to untreated SMA mice. However, motor performance did not fully recover to wild-type levels.

Importantly, patient-derived SMA type 3 fibroblasts mirrored the mitochondrial phenotype with increased Complex I activity and ROS, both of which were normalized to non-SMA fibroblasts by metformin treatment without any change in SMN protein levels. The human-cell data strengthen the translational relevance of our findings and support the notion of SMN-independent or complementary therapeutic opportunities. This study suggests mitochondrial dysfunction and oxidative stress as critical contributors to late-onset SMA pathology. The therapeutic potential of metformin as a complex I inhibitor offers a promising adjunct to existing SMN-enhancing therapies, particularly for late-onset SMA. Targeting mitochondrial pathways may mitigate oxidative damage and improve clinical outcomes, addressing a significant unmet need in SMA treatment.

P134

Dysregulation of neurotrophic B-Raf signaling by SMN depletion in an *in vitro* model of SMA

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Neurotrophic signaling regulates neuronal survival, differentiation, and plasticity through receptor-mediated intracellular cascades. The Ras/Raf/MAPK pathway plays a central role in transducing these neurotrophic cues into transcriptional and functional responses critical for neuronal development and maintenance. Previous studies have shown that SMN deficiency disrupts the neurotrophic B-Raf/14-3-3 signaling hub, likely compromising survival signaling in motor neurons. However, the molecular mechanisms remain poorly understood. To investigate the underlying mechanisms, we employed an ***in vitro*** SMA model using NSC34 motor neuron-like cells with a CRISPR/Cas9-mediated knockdown of SMN (SMN_{kd}). We assessed signaling changes through phospho-specific western blotting and analyzed gene and protein expression via qPCR and western blot, with a focus on the Ras/ B-Raf/MAPK pathway.

We found that SMN depletion induces widespread dysregulation in the signaling network surrounding B-Raf. These changes are associated with significant alterations in downstream Ras/B-Raf/MAPK pathway activity, as evidenced by shifts in phosphorylation levels of key signaling proteins, providing insight into how SMN loss contributes to impaired neurotrophic signaling.

P136

Motoneuron differentiation from iPSCs as a model for studying Spinal Muscular Atrophy

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Spinal Muscular Atrophy (SMA) is a hereditary neurodegenerative disorder marked by progressive motoneuron degeneration in the spinal cord, leading to muscle weakness and atrophy. The disease is caused by homozygous loss of function of the ***Survival Motor Neuron 1*** (***SMN1***) gene, which causes insufficient levels of the SMN protein. Although the molecular basis of motoneuron degeneration in SMA is not completely understood, disruptions in key survival signaling pathways have been reported in various SMA models.

Induced pluripotent stem cells (iPSCs) have emerged as a robust platform for modeling SMA and investigation of intracellular pathway alterations. Differentiation of iPSCs into motoneurons enables the study of neurodegeneration and motoneuron vulnerability at the cellular level.
This poster presents an optimized, stepwise protocol to generate mature human motoneurons from iPSCs derived from healthy individuals and SMA patients. The differentiation process involves sequential application of patterning factors and transcriptional regulators that guide cells toward mature motoneuron identity. The resulting neurons are validated by the expression of canonical markers, such as ChAT, III-Tubulin and Islet 1/2, as well as by morphological features consistent with motoneuron phenotypes, confirmed by electron microscopy.

Our results provide evidence of neurite degeneration and significant impairments in motoneuron survival and metabolism under conditions of cellular growth factor deprivation in motoneurons derived from SMA patients iPSCs. Neurite degeneration reflects progressive motoneuron damage, highlighting the combining impact of metabolism deficits and neurodegenerative processes on disease progression and motoneuron vulnerability. Increasing SMN levels may help ameliorate neurite degeneration and metabolic alterations, although additional targeted therapies may be required to fully address the multifaceted mechanism of SMA pathogenesis.

P138

Criteria for identification and precise quantification of spinal motor neurons in disease mouse models

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Motor neuron (MN) degeneration is a defining characteristic of MN diseases such as spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS). Accurate quantification of MN loss in mouse models is crucial for assessing disease progression and evaluating therapeutic interventions. In this study, we conducted a meta-analysis of 77 publications, revealing inconsistencies in spinal cord dissection specificity, the use of non-specific MN markers, and significant variability in reported MN loss within the same mouse models. These findings highlight the need for a standardized approach to MN quantification. To address this, we established key criteria for consistent MN assessment. First, we developed a spinal cord dissection protocol that enables segment-specific MN isolation and counting. Using ex vivo ventral-root back labeling and immunohistochemistry in combination with tissue clearing, we identified ChAT and HB9 as the only reliable markers for MN identification and further demonstrated that MN distribution varies across spinal segments. Second, we found that MN loss in SMNΔ7 mice is confined to specific MN pools and spinal segments, whilst significant MN loss was not evident in a proposed SMA Type 3 model throughout several spinal segments. Finally, we implemented a workflow that allows visualization of all MNs in a cleared spinal segment, followed by automated quantification using the open-source software Cellpose, ensuring objective and reproducible MN counting. Our study establishes a rigorous framework for MN identification and quantification in mouse models, providing a valuable reference for future research requiring precise MN counts.

P140

Treatment evolution in SMA: Insights from the SMArtCARE registry

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Following the sequential approval of nusinersen, onasemnogene abeparvovec (OA) and risdiplam, the SMA treatment landscape evolved over the past years. The aim of this study was to map the sequence and timing of SMA treatments using data from SMArtCARE, a disease-specific registry for patients with SMA across 84 participating centers in Germany, Austria, and Switzerland.

All patients registered in SMArtCARE were included in the analysis. Patients were grouped based on their treatment regimen. The impact of clinical and genetic factors on treatment decisions were evaluated, including age at start of treatment, ***SMN2*** copy number, motor milestones, the need for ventilator support or tube feeding, and the presence of scoliosis. Transition plots were created to demonstrate changes in treatment landscape over time across different subgroups.

A total of 2,140 patients were included. Of these, 744 patients (36.2%) switched DMT. Most treatments switches occurred shortly after approval of a new DMT. Among patients younger than three years, the most notable treatment shift occurred from nusinersen to OA, followed by patients shifting from nusinersen to risdiplam. In older children, a substantial number of patients switched from nusinersen to risdiplam – a trend that was also observed, though to a lesser extent, in adult patients.

In this large real-world cohort, we present the first comprehensive analysis of SMA treatment patterns across all age groups and disease severities. While most patients remained on monotherapy, switches were mainly observed in children and in the year following the approval of DMT.

P142

The comparative efficacy and safety of risdiplam versus high-dose nusinersen in children with Type 1 SMA

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Risdiplam and nusinersen are disease-modifying therapies approved for the treatment of spinal muscular atrophy (SMA). Type 1 SMA is a severe form of SMA and without treatment, infants fail to achieve major motor milestones and typically do not survive beyond 2 years of age. The efficacy of risdiplam and nusinersen have been established in children with Type 1 SMA in separate clinical trials. In the absence of head-to-head trials, indirect treatment comparisons adjusted for cross-trial differences can inform treatment decision-making.

The objective of this study was to compare the efficacy and safety of the approved risdiplam dose (0.2 mg/kg daily in children aged 2 months to <2 years; 0.25 mg/kg daily in children ≥2 years and <20 kg in weight) versus the investigational higher-dose (HD) nusinersen regimen (50/28 mg) in children with Type 1 SMA treated in clinical trials.

Patient-level risdiplam data were obtained from 58 children who received the pivotal dose in the FIREFISH clinical trial (Part 1 n=17, Part 2 n=41, NCT02913482) and published aggregate nusinersen data were obtained from 50 children in the DEVOTE clinical trial (Part B, infantile onset; NCT04089566).

Unanchored matching-adjusted indirect comparisons were used to compare outcomes between risdiplam and HD nusinersen groups with early-onset SMA, adjusting for age at first dose, disease duration, and Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) total score at baseline. Cox proportional-hazards models were used to compare overall survival and event-free survival.

After matching, relevant baseline characteristics were similar across groups. The effective sample size for risdiplam was 33.2, a reduction of approximately 43%. Compared with the HD nusinersen group (n=50), after 15 months of risdiplam treatment, the risdiplam group had a 75% reduction in the rate of death (95% confidence interval [CI] 11–93%) and a 76% reduction in the rate of death or permanent ventilation (95% CI 34–92%). While adjustments were made for known prognostic factors, as in any non-randomised comparison, results may be confounded by unobserved baseline differences between groups.

In this analysis, risdiplam was associated with lower risk of death or permanent ventilation when compared with HD nusinersen in children with Type 1 SMA in a period up to 15 months of follow-up. This comparative analysis leverages data from two robust clinical trial sources. Additional data sources should be consulted to expand on these findings.

P144

The integration of PROMs and real-world data: A holistic approach to characterise disease burden and treatment impact in spinal muscular atrophy

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The UK SMA Patient Registry, established in 2008, represents a well-defined cohort of individuals living with Spinal muscular atrophy (SMA) in the United Kingdom and Ireland. As of June 2025, the registry has 688 participants: 474 adults (≥16 years); 214 paediatric (<16 years). The SMA diagnosis is genetically confirmed in 452 (66%) of its participants. The registry is a valuable tool for the collection of SMA patient-reported outcomes (PROs) through patient-reported outcome measures (PROMs). PROMs capture the perspectives of people living with SMA about their quality of life and the impact of their condition.

In April 2022, the registry implemented the following PROMs:

- EQ-5D-5L
- EQ-5D-Y-3L
- Patient Global Impression of Severity (PGI-S)
- Patient Global Impression of Improvement (PGI-I)
- SMA Independence Scale – Upper Limb Module (SMAIS-ULM)
- Free-text box

The SMAIS-ULM is a PROM specifically developed for SMA, while EQ-5D PROMs are often used by regulators. The PGI scales are mandated by the TREAT-NMD SMA Expanded Core Dataset and so are used by many national SMA patient registries.

Since their implementation, PROMs questionnaires have been completed by 257 adults and by the caregivers of 106 paediatric patients in the registry. In total, the registry has collected 3764 responses to PROMs questionnaires.

In collaboration with the national SMA REACH clinical networks in the UK, PROMs data collected from patients receiving SMA treatment has been aligned with SMA REACH clinical data and submitted to UK regulatory authorities for consideration as part of the treatment reviews.

Correlations between patient-reported outcomes and patients' SMA type and functional status will be presented. PROMs asking directly about disease severity (PGI-S) received responses corresponding closely to patients' motor function ability, with lower-functional patients reporting greater severity. PROMs asking about mental health (EQ-5D-5L – 'anxiety/depression' dimension) or asking patients to score their overall sense of health (EQ VAS) received responses which showed stable scores across patients with varying levels of motor function.

The registry's presented data shows that PROMs add value to clinician-reported outcomes and offer a different perspective, demonstrating that it is worth continuing the effort of collecting the patient voice.

P146

Patient- and caregiver-reported swallowing and feeding outcomes in individuals with SMA treated with risdiplam: A longitudinal analysis of the Cure SMA Community Update Survey

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Spinal muscular atrophy (SMA) is a progressive neuromuscular disease associated with severe motor neuron degeneration, which causes, in addition to motor function impairment, bulbar dysfunction leading to swallowing and feeding difficulties. Clinical trials such as RAINBOWFISH (NCT03779334) and FIREFISH (NCT02913482) have provided key data on swallowing and feeding abilities in risdiplam-treated individuals with SMA, but real-world evidence is needed to better understand these outcomes. The Cure SMA Community Update Survey (CUS) is an annual survey of patient- and caregiver-reported data on health outcomes. This analysis describes swallowing and feeding abilities from the CUS in risdiplam-treated individuals with SMA.

Data were analyzed from individuals with SMA who completed the CUS between 2022 and 2024, had ≥2 CUS responses on swallowing and feeding abilities and indicated risdiplam as their most recent SMA treatment. CUS responses on swallowing and feeding abilities were retrospectively scored and adapted to the Children's Eating and Drinking Activity Scale (CEDAS) framework (scored from 1–6, with scores ≥4 as exclusive oral feeding) to describe changes in these abilities over ≤2 years of survey data.

The analysis included 107 risdiplam-treated individuals with SMA; 92 (86.0%) had 1 year of follow-up data on swallowing and feeding abilities, and 46 (43.0%) had 2 years of follow-up data. Mean (SD) ages were 4.2 (8.9) years at diagnosis, 22.0 (20.8) years at risdiplam treatment initiation, and 23.0 (20.8) years at baseline survey. The mean (SD) duration of risdiplam treatment was 14.1 (10.7) months. Most individuals (68 [63.6%]) were female, had two or three *SMN2* copies (34 [31.8%] and 45 [42.1%], respectively), and had been treated with other disease-modifying therapies prior to risdiplam treatment initiation (88 [82.2%]). At the time of the last survey, most individuals were able to sit without support (74 [69.2%]), and some individuals were able to stand and/or walk with or without assistance (20–37 [18.7%–34.6%]).
Of the individuals with 2 years of data, the frequency of exclusive oral feeding increased from 84.8% (n=39/46) at baseline to 87.0% (n=40/46) after 2 years. Analysis of CEDAS scores showed most individuals maintained their oral intake capabilities relative to their previous survey. The mean (SD) CEDAS score from baseline to year 1 and year 2 showed a small decrease of 0.1 (0.6) and 0.1 (0.7) points, respectively. For individuals with 1 year of follow-up data, 76.1% (n=70/92) were exclusively feeding orally at baseline and maintained this status.

This analysis of multiyear survey data from the CUS supplements existing clinical trial data, providing critical insights into swallowing and feeding abilities in risdiplam-treated individuals with SMA. The results of the analysis demonstrate maintained oral intake capabilities, addressing a significant unmet need in the SMA community.

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Validation and longitudinal progression of the Italian Spinal Muscular Atrophy independence scale – upper limb module: A two-phase study

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Spinal muscular atrophy (SMA) is a progressive neuromuscular disorder caused by SMN1 gene mutations. Despite therapeutic advances, traditional motor scales inadequately assess patient independence. This study validated the Italian Spinal Muscular Atrophy Independence Scale – Upper Limb Module (SMAIS-ULM) across SMA phenotypes.

Phase 1: Cross-sectional validation involved 472 questionnaires from 12 centers, including 263 caregivers (age 26.4±17.6 years; 29 SMA I, 123 SMA II, 104 SMA III, 7 presymptomatic) and 209 patients (age 33.1±16.4 years; 3 SMA I, 101 SMA II, 104 SMA III, 1 SMA IV) with 195 matched pairs. Analysis used intraclass correlation coefficients (ICCs), Kruskal-Wallis tests, and Spearman correlations.
Phase 2: Longitudinal analysis of 156 questionnaires from 78 matched pairs (patient age 32.3±17.5 years; 37 SMA II, 41 SMA III; mean treatment duration 3.94±1.97 years). Statistical analysis included Welch t-tests and Spearman correlations.
Phase 1: Test-retest reliability was excellent (ICCs: 0.97-1.00). SMAIS-ULM scores significantly differed by SMA type and motor function, with higher scores in SMA III/ presymptomatic and ambulatory patients ($p<0.001$). Floor effects occurred in 18.9% of non-ambulatory and 50% of ambulatory participants. Strong correlations with established functional measures were observed.
Phase 2: No significant difference in SMAIS score changes between patient and caregiver reports ($t_{(152.03)}=-0.08$, $p=0.94$; Hedges' $g=-0.01$). Caregiver-reported changes showed weak correlation with HFMSE changes ($=0.07$, $p=0.54$), while patient-reported responses showed modest positive correlation ($=0.25$, $p=0.028$). No significant correlations with RULM or 6MWT emerged.

The SMAIS-ULM demonstrates excellent reliability and validity for assessing functional independence across SMA phenotypes, with strong psychometric properties and applicability from both patient and caregiver perspectives. The scale effectively discriminates between disease subtypes and motor function levels, showing appropriate floor effects that mirror established outcome measures. The modest correlation between patient-reported SMAIS changes and HFMSE improvements suggests potential complementary value to traditional motor assessments. However, study limitations include that the mean treatment duration was of 3.9 years already at first assessment, potentially indicating therapeutic plateau effects that constrain longitudinal sensitivity. Future investigations will examine early treatment phases to better characterize responsiveness to therapeutic interventions.

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Patient-reported experiences with SMA therapies in North Macedonia: Results from a 2025 survey

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Spinal muscular atrophy (SMA) is a rare, progressive neuromuscular disorder that severely impacts motor function, independence, and quality of life. While novel therapies have transformed disease management, challenges remain regarding access, administration, and the psychosocial burden on patients and caregivers.

The study aimed to capture real-world experiences with SMA therapies, focusing on treatment effectiveness, mode of administration, logistical challenges, quality of life, and expectations for future therapie among SMA patients and their families in North Macedonia.

An anonymous online questionnaire was distributed to SMA patients and/or caregivers. The survey combined multiple-choice, Likert-scale, and open-ended questions to collect both quantitative and qualitative data on demographics, treatment satisfaction, daily challenges, and perspectives on new therapies. In August 2025, the patient organization STOP-SMA, in collaboration with a neurologist from the University Clinic of Neurology, conducted the survey.

A total of 21 respondents participated (38% patients, 62% caregivers). Most patients were adults (52%) and had been on therapy for more than 3 years. Oral daily treatment was the most common mode of administration (67%), followed by intrathecal injections (29%). Satisfaction with treatment was high: 81% reported being very or fully satisfied with effectiveness, and 71% with ease of administration. However, 57% reported practical difficulties such as travel to clinics, long waiting times, and the need for availability of special equipment. Moreover, 86% reported additional costs, including travel, accommodation, and loss of workdays. Treatment significantly improved quality of life in 57% of participants and had a positive psychological impact in 76%. Still, 40% had considered switching therapy, and 33% expressed interest in treatment switch, with greatest expectations linked to improved efficacy and motor function.

Patients and caregivers in North Macedonia generally report positive therapeutic outcomes but face significant logistical and financial burdens. The findings highlight the need for decentralized access, improved organization and reduced bureaucracy, and broader availability of new innovative therapies. Integrating medical, logistical, and psychosocial support is essential to optimize care and enhance quality of life for individuals with SMA.

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Patient experience in Spinal Muscular Atrophy clinical trials in Spain: A qualitative study from the perspective of participating families

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Clinical trial (CT) participation is essential for developing new therapies, but it also places a considerable physical, emotional, and logistical burden on participants and families. This study analyzes patient experiences to identify strengths, barriers, and opportunities for improvement within a patient-centered framework.

This qualitative study used online focus groups (OFG) and surveys with families from seven CTs. Testimonies from 29 families were gathered, 19 through OFG.

Regarding participation, families highlighted positive aspects such as access to potential therapies, expert multidisciplinary care in reference centers, and continuous follow-up until treatment approval.

In terms of treatment administration, participants valued strategies that reduced procedural burden, including nitrous oxide sedation for lumbar punctures and ultrasound-guided venipunctures performed by experienced staff. The accreditation of new CT centers closer to patients' homes also improved accessibility. Conversely, in some CTs, long and poorly structured hospital visits, delays in reimbursements, and lack of clarity about post-CT access to therapies were frequent sources of frustration.

For outcome assessments, families appreciated CTs where data were shared with regular care teams, reducing redundancy and supporting continuity. However, lack of access to individual results limited informed decisions about continuing, especially when beneficial pre-existing treatments (e.g., salbutamol) had to be discontinued. Dissatisfaction was frequent with functional scales that were lengthy, repetitive, and poorly adapted to SMA, failing to capture subtle improvements. In some cases, tests were administered by staff unfamiliar with SMA, adding fatigue and emotional burden. Families recommended integrating evaluations into physiotherapy, adopting PROMS, and exploring digital tools, including AI, to make assessments more relevant and less intrusive.

Additional challenges included unequal access to supportive care such as physiotherapy and inconsistencies between participants. Families stressed that to properly assess the effectiveness of experimental treatments, all participants must receive care consistent with Standards of Care (SoC). When insufficient access to physiotherapy is due to financial barriers, CTs should cover these measures as part of study costs. Families also called for updating the SoC to ensure that treatments commonly used in SMA practice can be continued during the trial.

The Spanish SMA research landscape shows strengths such as specialized networks, an engaged patient community, and increasing CT capacity. Yet CTs also place significant demands on families. Incorporating patient perspectives can reduce barriers, share best practices, and improve CT quality and adherence. Early engagement, realistic procedures, adapted assessments, updated standards of care, and transparent communication are essential for more ethical, effective, and sustainable research.

P154
Two game changing initiatives to support famillies
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To support families in their daily lives, AFM Téléthon has created two initiatives that are set to transform the way things are done.

The first is the individual support from professional experts called RPS ("Référent Parcours Santé", French for facilitator / integration technician). Fully created and funded by the association, their role is to help families cope with the disease on a daily basis. These 170 professionals, acting everywhere in France, support them at every stage of the disease, and ensure that patients receive responses tailored to their needs and are able to fulfil their life plans.Their support can include helping with administrative documents, accompanying patients to medical appointments, defining home adaptations, and even meeting school teachers or employers to explain the disease.

The second initiative enables families to enjoy a fully accessible holiday destination at a reasonable cost. These two respite homes, known as "Village Répit Famille ®" in French, are located throughout France and are designed to ensure the continuity of the care, while enabling the family caregivers to enjoy their holidays too. The fully accessible apartments sleep two to six people and have all the necessary medical equipment available on request (patient lift, medical bed, etc.). Patients can also request medical care, such as a nurse or physiotherapist, to ensure uninterrupted care. A variety of accessible activities are provided for patients, as well as opportunities for family members to relax (spa facilities, group discussions, etc.).

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The Brazilian national SMA registry: Integrating real-world evidence and advocacy to shape health policy

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Patient registries are critical tools to generate real-world evidence in rare diseases, supporting both clinical research and policy-making. In Brazil, the National SMA Registry, coordinated by INAME, has been instrumental in filling knowledge gaps on epidemiology, diagnosis, and access to care for Spinal Muscular Atrophy (SMA).

To present the evolution of the Brazilian SMA Registry and demonstrate how its data have contributed to regulatory and policy changes in access to treatment within the public health system (SUS).

Phase 1 of the registry (2021) collected data from 706 patients with a confirmed genetic diagnosis who responded to a questionnaire on natural history, genetic characteristics, drug treatment, and multidisciplinary care. Based on these responses, the researchers reached important conclusions about the distribution of SMA types, diagnostic delays, survival, and the impact of invasive ventilation and disease-modifying treatments, resulting in a peer-reviewed publication. The registry has remained active, and in September 2025, Phase 2 was launched. Designed with greater robustness, it investigates long-term follow-up and disease progression in patients undergoing treatment. This phase also addresses topics that were not available a few years ago, such as the identification of patients diagnosed through expanded newborn screening, which is still currently under implementation. To date, approximately 300 patients have responded to Phase 2, which aims to monitor the progression of patients who already participated in Phase 1, identify new patients, and includes a questionnaire specifically designed for caregivers.

Registry data have directly informed advocacy and policy decisions in Brazil:

- **2019:** Demonstrated that only 5 patients (<0.6%) met CONITEC's (National Commission for the Incorporation of Technologies into the Brazilian Unified Health System) preliminary recommended criteria for nusinersen treatment leading to expanded access recommendations with no age limit.
- **2021:** Showed that mean age at diagnosis for type 2 SMA was ~3 years, while symptoms emerged by 18 months; this evidence supported a policy change to include patients with "symptom onset before 18 months," rather than "diagnosis before 18 months."
- **2025:** The registry was cited in CONITEC's preliminary recommendation report on nusinersen for SMA type 3, with prevalence estimates based on registry data (160 patients with type 3 in Brazil).

The Brazilian SMA Registry exemplifies how real-world data can bridge the gap between patient experience and health policy. Beyond providing epidemiological insights, it has become a strategic tool for advocacy, ensuring that access decisions reflect the actual needs of the SMA community.

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Onset of scoliosis in patients with Spinal Muscular Atrophy Type 1 (SMA 1): A single-center clinical experience

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Disease-modifying therapies (DMT) in SMA 1 have significantly improved survival and motor outcomes. However, musculoskeletal complications, particularly scoliosis, remain a major clinical concern.

Retrospective analysis of a cohort of 9 patients with SMA 1, followed at the SMA Clinic of Agia Sofia Hospital.

We studied 9 patients with SMA 1 carrying 2 copies of ***SMN2***. The mean age was 4.4 years (SD 2.7). Two patients received DMT at 3 weeks of age, one asymptomatically and the other oligosymptomatically. Among symptomatic patients, the mean age at DMT initiation was 7.5 months (range 2–24 months). Gene therapy was the initial treatment in 6 patients, while 3 received nusinersen, of whom 2 subsequently transitioned to gene therapy. All patients were started on physiotherapy at the time of diagnosis. Scoliosis developed in 8 of the 9 patients. The only patient without scoliosis was a 3.5-year-old walker who had received presymptomatic therapy.
Three patients developed scoliosis within the first 6 months of life; they had started DMT at a mean age of 4.7 months (range 2–8.5 months), were all sitters, and 1 required nocturnal invasive ventilation. Two patients developed scoliosis between 6 and 12 months of age; they had initiated DMT at 0.7 and 2.8 months, were a walker and a sitter respectively, and neither required respiratory support. The remaining 3 patients developed scoliosis after 12 months of age; they had started DMT at a mean age of 12 months (range 5–24 months), were all sitters (2 also standers), and all required nocturnal ventilatory support (1 invasive and 2 with BiPAP).
Spinal bracing was initiated in 7 patients at a mean age of 2.6 years (range 0.5–7.5 years). In 2 patients, aged 6 and 5.5 years, surgical management is currently being planned.

In our cohort of SMA 1 patients, despite early initiation of DMT, scoliosis often developed early in life. Interestingly, patients who initiated treatment later also developed scoliosis later, and all were on respiratory support. This observation may reflect differences in early motor activity, positioning, or disease severity, although the underlying mechanisms remain unclear.
Our findings suggest that despite early and universal access to novel DMT and supportive care such as physiotherapy and spinal bracing, scoliosis remains a highly prevalent and significant comorbidity in SMA 1. These therapies may not prevent the development of severe spinal deformity, underscoring the need for proactive orthopedic monitoring and management from a very young age.

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Real-time digital measurement of patient-experienced outcomes: An intensive longitudinal study in adults living with spinal muscular atrophy

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There is a growing recognition that internal, patient-experienced outcomes such as fatigue and pain play an important role in the general well-being of people living with SMA and might be valuable as outcome measures for new treatments. So far, these internal experiences have been measured with global self-report questionnaires that retrospectively assess how patients felt during a specified period. However, evidence from psychological science suggests that retrospective self-reports cannot fully capture these internal states due to their rapidly fluctuating, dynamic nature. In addition, memory biases lead to inaccurate self-reports. The aim of this study was to assess whether it is possible to collect patient experience data in adults living with SMA through intensive longitudinal real-time digital measurements.

We conducted an ecological momentary assessment (EMA) study in 36 adults with SMA (M_{age}=36). The study consisted of a pre- and post-measurement, and 10 days of intensive longitudinal assessment of patient experience outcomes. Participants were prompted six times a day for ten consecutive days to respond to an electronic questionnaire through a smartphone application. The study included measures for somatic experiences (e.g., fatigue and pain) as well as psychological (e.g., emotions and self-esteem), social (e.g., interactions with others), and contextual (e.g., location and work) factors.

On average, participants responded to 76.9% of the prompts. Participant feedback indicated that the research method was not perceived as too burdensome, and many found it beneficial to track their symptoms. In addition, intra-class correlations indicated that there is a large amount of intra-individual variability (40-60%) in how internal states are experienced. This indicates that individuals with SMA do not only differ from each other in their experiences of for instance fatigue and pain, but that these experiences also considerably fluctuate over time within individuals.

This study shows that it is feasible for people with SMA to participate in intensive longitudinal data collection. In addition, many outcomes appear to have large within-person variance, which is impossible to capture with the currently used retrospective self-report questionnaires. Together, these findings imply that to understand and measure patient-experience outcomes such as fatigue and pain in a meaningful and ecologically valid way, real-time digital assessment is needed.

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Moving beyond types and motor milestones: The need for a new disease-description framework for spinal muscular atrophy in the era of disease-modifying therapies

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The historical classification of spinal muscular atrophy (SMA) into discrete "types" based on age at symptom onset and highest achieved motor milestone has long served as a diagnostic and prognostic tool. However, its prognostic value has always been limited, and the advent of disease-modifying therapies (DMTs), the implementation of newborn screening, the improved standards of care, and growing recognition of SMA as a multisystem disorder have reduced the usability of this classification system. Here, we discuss several limitations of type-based classification. First, types are static and retrospective, offering little insight into an individual's current status. Second, motor abilities exist on a continuum, and intra-type variation can exceed differences between types. Third, the system oversimplifies motor function, overlooking abilities central to independence. Finally, it fails to capture non-motor manifestations of SMA. Data from SMA Europe's 2025 pan-European community survey provide evidence for these limitations, with respondents reporting that their lived experience does not align with static type categories, reflecting overlapping motor and non-motor challenges that evolve over time.

A rigid classification system such as the type-based has also carried critical real-world consequences in the era of DMTs. As it formed the foundation of early clinical trials, it directly shaped trial design, endpoints and participation criteria. Subsequent health technology assessment and reimbursement processes relied on the same framework, thereby reinforcing access inequities not only for patients who never fit neatly into these categories, but also for those whose disease trajectory shifted them across categories over time. As the system remains in place, newer trials have been obliged to adapt to these predefined "boxes," rather than reflect the true continuum of abilities and needs within SMA. As a result, this restricts access, leaves limited evidence regarding efficacy and safety for individuals with non-prototypical clinical presentations, and produces real-world evidence that diverge from clinical trial data. In addition, in clinical practice, static types seem to provide little guidance for management, leaving decisions heavily dependent on individual clinician judgement.

We call for the development of an updated framework. Such a system is essential not only for accurate clinical description and guidance, but also to promote more equitable access to therapies across diverse healthcare systems. Such a system should: include all clinically and patient-relevant domains and recognise them along a continuum rather than within rigid categories; capture both past and present clinical state and describe symptom trajectory; allow individualisation by symptom combinations, severity, rate of change and patient priorities; and remain adaptable to future scientific discoveries.

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Experiences of clinical trial participation in SMA: Insights from a Pan-European SMA Europe survey

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Clinical trials are vital to the continued development of new and improved medicines for SMA. With three disease-modifying therapies for SMA now on the market and new compounds in clinical trials, SMA Europe's EUPESMA 2023 Survey on SMA and Clinical Trials sought to understand 1) whether people living with SMA and their families are still willing to participate in clinical trials and think there is still a need for new medicines and clinical trials for SMA, 2) what their experiences and expectations are, and 3) what challenges they may face in regard to clinical trial participation. The survey was open to people living with SMA (16 years old or older), their parents or caregivers, with and without previous clinical trial participation experience, and available in 14 European languages.

We received survey responses from people living with SMA themselves (52%, n=447) and caregivers of people living with SMA (45%, n=389). The respondents represented a range of demographics (age range 1-79 years, M = 23,9, SD = 18,8; sex: female, 56%, n=435, male, 41%, n=318) and disease-severity levels (walkers, 16,8%, n=110; sitters, 47,1%, n=309; non-sitters, 36.1%, n=237). Our findings show that people living with SMA and their caretakers agree that there is a need for new medicines (98%, n=629) and for new clinical trials in SMA (97%, n=623). A vast number of participants (87%, n=559) reported that they would be willing to participate in a clinical trial. Yet most (70%, n= 457) reported that they never had this opportunity, although they would have wished to participate. Indeed, only 20.6% (n=134) had participated in a clinical trial before, and only 9.4% (n= 61) declared they never participated because they did not want to.

The survey investigated the experiences of participants with previous clinical trial experience to show how clinical trial participation can be made more patient-friendly, ensuring people living with SMA continue to be willing to participate in clinical trial s. These measures include improvements to the infrastructure, services and cost coverage for clinical trial participants. For participants without clinical trial experience, our analysis focuses on challenges to clinical trial participation and reasons for not participating to suggest patient-centric ways to overcome these obstacles.

Our data shows that there is high need for clinical trials and clinical trial participation in the SMA community in Europe. Opportunities for participation, however, are limited and challenges persist. A patient-centric and patient-friendly approach to clinical trial design may mitigate issues in recruitment and retention of clinical trial participants, ensuring that clinical trials can successfully conclude.

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The OdySMA Nations League: Descriptive benchmarking of system-level access to therapies and care across Europe

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SMA Europe, the umbrella organisation of European spinal muscular atrophy (SMA) patient organisations, works to ensure equitable access to diagnosis, treatment and care for all people living with SMA. To support this mission, SMA Europe launched ***OdySMA - a quest to access***, a participatory monitoring platform designed to capture and visualise system-level access data. One of its core components, the ***Nations League***, provides a comparative benchmark of country performance across Europe.

The Nations League currently includes 27 European countries, each evaluated across 13 indicators reflecting the SMA care pathway: newborn screening (NBS), availability and reimbursement of the three authorised disease-modifying therapies (DMTs), early access programmes, reimbursement criteria, adult care services, registries, and governance structures. Indicators and scoring were co-developed with patient organisations and health policy and health economics experts. Indicators are scored as ***Good*** (1 point), ***To improve*** (0.5), or ***Not authorised/not available*** (0). The maximum possible score is 14. Whereas SMA Europe's community surveys and real-life stories capture the experiences of individuals and families, the Nations League complements this by assessing system-level policies, pathways and infrastructures.

For 2025, scores varied widely, from near-maximum in the highest-scoring countries to less than half of the possible points in the lowest. Most countries performed well on therapy authorisation, but marked inequities were seen in reimbursement criteria (with age or tracheostomy frequently used as exclusion criteria), in the uneven rollout of NBS, and in the organisation of adult care. Illustrative contrasts show that some high-GDP countries underperform relative to peers, while some lower-GDP countries achieve comparatively higher access, underlining the role of policy choices and rare disease governance.

The Nations League provides the first patient-led, participatory and system-level benchmark of SMA access across Europe. By linking health system structures to access indicators, it complements access data with insights into real-world implementation. For healthcare professionals, inequities in NBS and reimbursement criteria are directly relevant, as they determine timely diagnosis and initiation of DMTs, both critical to clinical outcomes. Beyond description, transparent benchmarking motivates peer accountability and equips clinicians, policymakers and advocates with community-driven evidence to reduce inequities in SMA care, advancing SMA Europe's vision that no one is left behind.

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From questions to impact: Community-driven research priorities in SMA

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Spinal Muscular Atrophy (SMA) is a progressive, degenerative neuromuscular condition that continues to face structural challenges in securing sufficient research funding and resources. Although three disease-modifying therapies have become available and have transformed the clinical trajectory of SMA, the condition remains uncured and significant unmet needs persist across multiple domains in daily life. In this evolving scientific and clinical landscape, aligning research priorities with patients' lived experiences is increasingly recognised as essential to ensure that investments deliver meaningful, community-relevant outcomes. Patient and Public Involvement (PPI) is a well-established approach that helps embed these perspectives into research and policy decisions, leading to more patient-centred outcomes.

To this end, SMA Europe, a non-profit umbrella organisation of SMA patient organisations in Europe, initiated a multinational research priority-setting process. At its core was a Priority Setting Partnership (PSP), conducted using the James Lind Alliance methodology, to identify the "Top 10" unanswered research questions in SMA from the perspectives of patients, caregivers, and healthcare professionals. This was followed by two additional phases: engagement with the broader research and clinical community to contextualise and enrich these priorities through expert dialogue; and dissemination of the outcomes to raise awareness, establish a feedback loop with the community, and stimulate research and funding activity. More broadly, the initiative aimed to demonstrate how participatory approaches can shape the rare disease research agenda.

Over 900 participants from 22 countries submitted priorities, which were consolidated and ranked through multilingual surveys and a final consensus workshop to produce a community-defined "Top 10". These priorities cover areas such as motor unit regeneration, biomarkers, personalised physiotherapy, nutrition, fatigue, and assistive technologies. While some align with ongoing research, others highlight underexplored areas that are central to quality of life. In phases 2 and 3, SMA Europe convened a transdisciplinary expert workshop to explore these priorities in depth and launched a dissemination campaign to promote uptake among researchers and funders.

This participatory process underscores the role of patient organisations as conveners and co-creators in shaping research strategy. The resulting Top 10 priorities now guide SMA Europe's research agenda and offer a replicable model for funders and researchers seeking to align innovation with community-defined needs.

P170 - FLASH TALK

Proteomic profiling of cytoplasmic stress-induced liquid condensates of SMN

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The survival of motor neuron (SMN) protein, best known for its role in spinal muscular atrophy (SMA), is essential for assembling uridine-rich small nuclear ribonucleoproteins (UsnRNPs) for RNA splicing. SMN functions as part of a macromolecular complex with Gemin2–8 and UNRIP, facilitating snRNP assembly in both the cytoplasm and nucleus, where it condenses into nuclear Cajal bodies through liquid-liquid phase separation (LLPS) in an mTOR-dependent manner. SMN also participates in the formation of cytoplasmic stress granules (SGs) via RNA-binding regions. However, the role of SMN's LLPS capacity in cytoplasmic processes remains poorly understood.
Here, we show that hyperosmotic or mechanical stress induce the formation of cytoplasmic SMN condensates, termed **S-bodies**, in human cells. Live-cell imaging reveals that S-bodies are dynamic, rapidly moving along microtubules during stress, and are distinct from SGs, incorporating additional proteins and RNAs beyond the canonical SMN complex. Notably, the SMA-linked SMN variant lacking exon 7 (SMNΔEx7), which lacks LLPS capability, fails to form S-bodies and instead preferentially accumulates in SGs during stress recovery. In mouse embryonic fibroblasts (MEFs) modelling SMA, treatment with the approved SMA drug Risdiplam restores LLPS ability, enabling efficient S-body formation.

During recovery, SMN forms Janus-like droplets with CLNS1A, suggesting a regulated molecular handoff that facilitates the repair or rebuilding of snRNPs after stress. Proteomic analysis of isolated S-bodies using proximity labeling and sedimentation approaches reveals that these condensates are enriched in RNA helicases, indicating a role in RNA metabolism.

Our findings identify a novel cytoplasmic function of SMN in the formation of stress-induced S-bodies, which appear to transiently arrest and reactivate key steps in snRNP biogenesis during stress. These results suggest that defective phase separation of SMN underlies SMA pathology, implicating SMA as a disorder of impaired LLPS.

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Role of SMN protein in nucleolar homeostasis following DNA damage

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In the nucleus, the Survival Motor Neuron (SMN) protein localizes to Cajal bodies (CBs), which are functionally connected to nucleoli. The nucleolus is a membraneless organelle with a highly organized architecture essential for ribosome biogenesis, including transcription of ribosomal DNA (rDNA) by RNA polymerase I (RNAP1) and early pre-rRNA processing. This organization can be dynamically perturbed by genotoxic stress.

We show that following UV-induced DNA damage, RNAP1, Fibrillarin (FBL), and rDNA are displaced from the nucleolar center to the periphery to enable DNA repair. Full restoration of nucleolar structure occurs only after complete repair of DNA lesions, independently of rDNA transcription resumption.

Our results reveal that SMN, together with proteins such as FBL and COILIN (COIL), plays a critical role in re-establishing nucleolar organization after genotoxic stress. In SMN-deficient cells (shSMN-expressing fibroblasts, SMA patient fibroblasts, and SMA iPSC-derived motoneurons), nucleolar proteins (RNAP1, FBL) fail to return to their correct nucleolar position after DNA repair. Defective nucleolar homeostasis in these cells correlates with increased sensitivity to DNA damage.
Unexpectedly, we observed that in wild-type cells, SMN and its partners relocalize from CBs to nucleoli during DNA repair. This shuttling depends on COIL and on PRMT1 activity, which arginine-methylates SMN partners. Once repair is completed, SMN returns to CBs in a process that requires FBL. In the absence of COIL or FBL, SMN interactions with its partners are disrupted.

Altogether, our study uncovers a new molecular function of SMN in nucleolar homeostasis after DNA damage. This function may represent an unexplored contribution of SMN deficiency to the cellular pathology of spinal muscular atrophy (SMA). As a next step, we are currently identifying and characterizing the partners of SMN involved in this process, and assessing their impact on nucleolar organization and on SMN relocalization during genotoxic stress. In parallel, we are validating this newly identified nucleolar function of SMN in post-mitotic cells as well as during cellular differentiation.

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SMN-independent rescue of spinal muscular atrophy by small drug compounds

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Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disorder caused by mutation of the ***survival motor neuron 1*** (***SMN1***) gene. SMA is characterized by degeneration of the spinal cord motor neurons caused by chronic low levels of survival motor neuron (SMN) protein. Prevention or slowing of neurodegeneration has been shown to ameliorate SMA disease severity. Significant progress has been made to develop SMN-dependent treatments that increase SMN levels. However, there is an unmet need to develop alternative therapeutic methods that are SMN-independent. The c-Jun-NH_2 terminal kinase (JNK) signaling pathway mediates motor neuron degeneration in SMA. Genetic inactivation of the neuron-specific isoform, JNK3, ameliorates the disease phenotype in SMA mice without affecting SMN protein levels, indicating that JNK3 may represent a promising SMN-independent target for pharmacological intervention. We report that pharmacological inhibition of JNK using novel drug compounds based on three distinct chemical scaffolds, Anthrapyrazolone, Pyrimidinyl, and Pyridopyrimidine, prevents degeneration of SMN-deficient cultured primary neurons and spinal cord motor neurons derived from SMA mice ***in vitro***. Furthermore, ***in vivo*** treatment with JNK inhibitors leads to a systemic improvement in the disease phenotype, promoting enhanced overall growth, including increased body weight and extended postnatal growth, alongside improved gross motor functions such as righting reflexes and the ability to walk until the later stages of survival. Notably, it also results in a significant and sustained increase in the lifespan of both male and female SMA mice. The sex-based analysis reveals male- and female-specific improvements that depend on the type and efficacy of inhibitors targeting distinct JNK isoforms. Importantly, treatment with JNK inhibitors did not affect SMN levels in the spinal cord or skeletal muscle, indicating that the observed rescue of the SMA phenotype occurs independently of SMN restoration. Collectively, these findings suggest that pharmacological inhibition of JNK may serve as a therapeutic strategy to prevent neurodegeneration, either in combination with SMN-enhancing approaches for treating severe forms of SMA, or as a stand-alone, SMN-independent intervention for moderate and mild SMA cases.

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Generation of novel *Drosophila* models for the study of the NEDCAM disease

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After decades of research aimed at understanding the autosomal recessive neurodegenerative disease Spinal Muscular Atrophy (SMA) as well as its underlying mechanisms and successful development of multiple therapeutic approaches, interest in investigating possible links of other members of the SMN complex to human disease has increased. One of these members is GEMIN5, a multifunctional protein capable of binding snRNAs and promoting their assembly into snRNPs by the SMN complex. Remarkably, recent studies have identified biallelic variants in the ***GEMIN5*** gene as the cause of a human inherited disorder with clinical features distinct from SMA, now known as Neurodevelopmental Disorder with Cerebellar Atrophy and Motor Dysfunction (NEDCAM). Additional research indicating that ***SMN*** overexpression may rescue the phenotype of GEMIN5 depletion in ***Drosophila*** models suggested an eminent reciprocity between SMN and GEMIN5 ***in vivo***. To address the lack of reliable NEDCAM models, we are generating a CRISPR/Cas9 ***GEMIN5*** knock-out and knock-in allelic variants in ***Drosophila*** that allow the study of wild-type and pathogenic forms of the GEMIN5 protein under physiological conditions.

We confirmed previous findings showing early lethality associated with ubiquitous or pan-muscular RNAi-mediated knock-down of ***GEMIN5*** in fly models as well as severe eye degeneration following ectopic knock-down. Additional morphological studies showed a significant reduction of bouton size at neuromuscular junctions (NMJs) in L3 larvae with ubiquitous ***GEMIN5*** knock-down. Next, we will test if ***SMN*** overexpression is able to rescue the observed phenotypes. Furthermore, we have generated a heterozygous knock-out allele of ***GEMIN5*** in ***Drosophila*** and are in the process of establishing different knock-in lines including those with point mutations known in humans and conserved in flies.

This approach provides a foundation for mechanistic studies of GEMIN5 mediated neurological disease and for investigating the efficacy of SMN-inducing strategies for NEDCAM therapy.

P178

SmF^{D37N} suppresses SMN^{E134K} loss of function by enhancing Sm-ring assembly activity

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SMA is caused by SMN protein deficiency. SMN has been shown to effectuate multiple functions, either individually or as part of multimeric complexes within the cell, including assembly of the spliceosomal UsnRNPs. Whether SMA results from deficiency of one, or several, SMN functions remains elusive. Here, we show that a single point mutation in the core spliceosome component SmF rescues the loss of function observed in the pathological SMA mutation E134K in SMN (SMN^{E134K}). In conjunction with a detailed biochemical investigation of the mutant proteins, our findings support the notion that defects in the UsnRNP assembly pathway contributes to the SMA etiology.

SMN is encoded by two genes in humans, ***SMN1*** and its paralog ***SMN2***. SMA results from truncations, deletions and/or missense mutations in the ***SMN1*** gene and insufficient functional SMN produced by ***SMN2***. Disease severity varies significantly, depending on the nature of the ***SMN1*** mutation and the abundance of functional SMN produced from ***SMN2***. Mice have a single SMN producing gene, ***Smn1***. We previously showed that Cre-mediated excision of ***Smn1 exon 7*** (to SMNΔ7) in cells is lethal. Expression of SMN missense mutants—including the severe SMN^{E134K}—fail to rescue this lethality. We used this system to identify genomic mutations that rescue cell viability when only SMN^{E134K} and mouse SMNΔ7 are expressed. Whole genome sequencing of five independent clones identified SMN complex components, Gemin2, 3, 5 and SmF, as candidate suppressor genes. Among these candidates, only the SmF mutant D37N rescued survival, when expressed in the presence of SMN^{E134K}.

SmF is part of the Sm core domain that assembles as a ring at the Sm-site on spliceosomal UsnRNPs in a reaction catalyzed by the SMN complex. This assembly reaction involves the handoff of pre-assembled Sm-protein subcomplexes from the PRMT5 complex onto the SMN complex, followed by delivery onto the UsnRNAs. The biochemical reconstitution of the assembly reaction revealed that double mutant complexes comprising SMN^{E134K} and the suppressor SmF^{D37N} facilitated a more efficient transfer of the Sm core onto the UsnRNA. Dissection of individual steps of the assembly reaction showed that the handoff of Sm-proteins to SMN^{E134K} and/or SmF^{D37N} containing complexes was unaffected. However, SMN^{E134K} and SmF^{D37N} conditions yielded significantly more assembled UsnRNPs within a shorter time frame as well as lower concentrations of the SMN complex.

These data strongly implicate reduced UsnRNP assembly activity as the root cause of SMA disease onset in the case of SMN^{E134K}. Transgenic mouse experiments to rescue SMN^{E134K} pathogenicity with SmF^{D37N} are ongoing. Understanding individual molecular mechanisms underlying SMA pathology will be a key factor in developing alternative therapeutics for the future.

P180

Family relocation in Spinal Muscular Atrophy: SAPRE centre experience over the last decade

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Families of children with Spinal Muscular Atrophy (SMA) often relocate due to a lack of adequate healthcare resources, limited access to approved treatments, a desire to improve their child's and family's quality of life, and, in some cases, political instability or war. Over the past decade, the SAPRE (Family-Centered Service) in Milan has supported over 100 families, predominantly from Eastern Europe. Despite significant international therapeutic advancements, their continued arrival highlights persistent, unmet needs in their home countries. This phenomenon suggests that patient needs extend beyond the purely medical realm, underscoring the importance of comprehensive care models that also account for the patient's quality of life.

This study aims to demonstrate that the migratory motivations of families with SMA-affected children are not limited to accessing pharmacological protocols. The analysis highlights the growing importance of "global care" that includes socio-economic integration, social inclusion, and the acquisition of skills for managing the daily aspects of the disease, underscoring the need for an approach that integrates quality of life into standard care models.

This study was conducted on 100 migrant families who received care at SAPRE over a ten-year period. The families had children diagnosed with SMA types 1 (75), 2 (24), or 3 (1). Each family submitted an internal multiple-choice questionnaire to explore their motivations, needs, and expectations related to their migration to Italy. All families participated in the PAPG (Parent Early Empowerment Program), which aims to increase caregivers' and individuals' competence and awareness in managing SMA in daily life.

The questionnaire analysis reveals the sustained nature of the migratory phenomenon over the last decade. Findings indicate a shift in migratory priorities over time: while ten years ago the primary motivations were related to access to pharmacological treatments and better healthcare, today there is a partial overlap between primary and secondary needs. Current families consider both optimal healthcare and the acquisition of strategies and skills for daily life in an inclusive community setting to be of equal importance.

Migration is not merely a search for medical treatment but a clear indication that families seek comprehensive assistance. Findings show that the needs for socio-cultural integration and the learning of best practices for disease management have become crucial factors. It's concluded that to effectively address the challenges of SMA, it's essential for care standards to integrate the patient's quality of life, recognizing the importance of an integrated approach that supports the entire family within its social context.

P182

Budget impact analysis of Risdiplam for the treatment of patients with Spinal Muscular Atrophy (SMA) in Colombia

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Spinal muscular atrophy (SMA) is an autosomal recessive disease caused by mutations in the SMN1 gene on chromosome 5, resulting in reduced expression of the survival motor neuron protein (SMN). This causes progressive muscle atrophy and weakness of several muscles. Risdiplam is an orally administered therapy that modifies pre-mRNA splicing of the survival of the motor neuron 2 (SMN2) gene and has shown significant improvements in motor function and achievement of developmental motor milestones in types I-III.

We evaluated the budgetary impact of risdiplam for patients with SMA, compared to Nusinersen, best supportive care and gene therapy AVXS-101. We adopted the perspective of the General Social Security Health System in Colombia, with a 3- and 5-year time horizon (2024-2028), following the guidelines of the national Health Technology Assessment Agency. Costs are shown in 2024 USD (1 USD=4071 COP).

The model used the eligible population based on Colombia's demographic data and the expected increase and prevalence of SMA. Healthcare resources (HCR) considered were acquisition and administration costs, concomitant medications, adverse events and other HCR (consultations, diagnostic tests, procedures) required in the care of SMA patients. HCR were estimated based on the administration route, validated with local clinical experts and complemented with national sources. Dosage information was based on weight and age as reported in national surveys and was adjusted to account for the lower weight observed in SMA patients.

The model compares two scenarios: one with the progressive adoption of risdiplam, versus one without it. The main outcome of the analysis was the yearly budget impact of using risdiplam in the treatment of SMA.

A total of 295 patients, which increased to 330 by 2028, were modelled. At birth, the distribution of SMA types was 60% (Type I), 28% (Type II) and 12% (Type III). Risdiplam results in considerable savings compared to nusinersen, particularly for Type I SMA patients, with first-year savings of over $232,000 per patient. Although the cost of nusinersen decreases after the loading dose, risdiplam continues to provide a significant budget impact reduction. The use of risdiplam generates total savings of $3.6 and $7.1 million over three and five years, respectively, resulting in a 6% cost reduction. Savings were mainly driven by reductions in acquisition and administration costs.

Risdiplam offers substantial reduced expenditure for the Colombian National Health System due to its lower acquisition and administration costs compared to other treatments for Type I and Type II SMA, establishing its role as a disease-modifying therapy that represents a cost-saving alternative for the management of SMA.

P184

Understanding physical therapist perspectives on the clinical meaningfulness of 'any point differences' on the Hammersmith Functional Motor Scale-expanded in SMA

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Spinal muscular atrophy (SMA) is a severe neuromuscular disorder marked by permanent loss of spinal motor neurons, progressive muscle atrophy, and weakness, which leads to motor function decline. Functional assessments (eg, HFMSE, MFM-32) are important tools for analyzing treatment efficacy over time; however, determining clinically meaningful changes can be challenging and often require input from patients or their caregivers.

To gain insight into how functional changes measured by the HFMSE are perceived in terms of clinical meaningfulness, we conducted 60-minute semi-structured interviews with patients, caregivers, and providers, including neurologists and physical therapists (PTs) with experience in both treating SMA and using the HFMSE.

We present findings from nine interviews with PTs, highlighting their perspectives on what defines clinically meaningful change within the HFMSE. The discussions also explored which functional tasks best represent such meaningful improvements.

For PTs, the most common clinical setting of practice was a health system/hospital-based outpatient clinic (6/9; 66.7%). The percentage of time per week PTs reported they spend treating patients ranged from 0-49% (3/9; 33.3%), 50-79% (3/9; 33.3%), and ≥80% (3/9; 33.3%). All PTs indicated they were 'very familiar' with the HFMSE (100%) and reported receiving structured training on how to administer the assessment (100%). When defining clinically meaningful change, PTs had slightly more specific criteria than the 11 neurologists we interviewed; they stated it should reflect true functional improvements that can be repeated, are relevant to the patient, and improve quality of life. Overall, PTs noted that clinically meaningful tasks differ by age and functional level; however, PTs also emphasized that any point improvement across HFMSE tasks are meaningful as they could bolster patient morale by enhancing independence and quality of life. For example, one PT noted that small improvements in the rolling task would be a "game changer" as patients would not have to ask for as much assistance. When focusing on transitioning from lying to sitting, another PT stated, "[Improving from] a 0 to a 1 is a big deal..." as it would enable patients to regain their independence and confidence.

According to PTs, clinically meaningful change should reflect repeatable functional improvements that are relevant and meaningful to a patient. PTs recognized that individual score improvements of any point magnitude on the HFMSE are meaningful, as these changes could augment patient independence, engagement in meaningful activities, and overall quality of life. Furthermore, because motor function tools like the HFMSE are key for evaluating treatment outcomes, understanding their clinical meaningfulness for individuals is essential and assist in relating point changes to real-world differences in independence, activities of daily living, and/or quality of life.

P186

Gait in Spinal Muscular Atrophy (SMA): A case series of adults with Type 3 SMA

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The phenotype of Type 3 SMA is varied with some people mobilising independently, whilst others may lose ambulation during their teenage years. Describing this variation in gait can be difficult, but gait kinematics can provide further information. The SMA clinic was established at St George's Hospital in London in 2020. As part of clinical practice, ambulant adults with Type 3 SMA have routinely been assessed in the gait laboratory. Specific gait assessments occur every 12-18 months.

Gait kinematics can help to describe the different gait characteristics in a heterogeneous group, such as Type 3 SMA, especially where patients are scoring highly on more traditional outcome measures. It allows a more detailed description of gait as well as providing additional outcome measures with which comparison can be made throughout disease modifying therapy. It can also be used to inform new clinically relevant outcome measures in Type 3 SMA.

This builds on previously reported data of three patients with baseline assessments. Currently, seven ambulant adults have had an initial gait assessment and four have had a follow up gait assessment after a 12–18-month period. Of those four adults, three have had a third gait assessment.

Distance walked during the 6-minute timed walk ranged from 42m to 575m across the seven adults. Across the cohort, findings that appear characteristic of SMA type 3 have been identified including reduced stance phase hip extension and reduced loading response of the hip and knee. A detailed case series will be described.

Findings suggest that detailed gait analysis may be useful in identifying small changes over time that traditional outcome measures aren't able to capture.

P188

Minimal clinically important difference on the revised Hammersmith Scale for Spinal Muscular Atrophy

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The Revised Hammersmith Scale (RHS) is a validated outcome for gross motor function in Spinal Muscular Atrophy (SMA) increasingly used both in clinical practice and clinical trials. To understand the impact of changes in the RHS, meaningfulness of these changes for individuals with SMA and their families must be established. Currently there is a lack of understanding of the RHS MCID for individuals with SMA. The objective of this analysis is to determine RHS MCID within different populations of those with SMA.

Parents/caregivers of individuals diagnosed with SMA at Great Ormond Street Hospital, UK, and individuals with SMA over 13 years old were invited to participate. Physiotherapists administered a questionnaire investigating what changes in physical activities related to RHS items would represent a meaningful impact on their child's/ their daily activities if it occurred. A numerical analysis of MCID will be performed, comparing perceived trajectory over the last year with actual change on the RHS. A qualitative analysis will also be undertaken via focus groups to allow for more focused perception of meaningful change related to functional changes.

Recruitment is ongoing for this study. At this interim analysis, 20 parents and 2 individuals with SMA have completed the questionnaire. For all included participants (via parent and self-response), the median (IQR) age was 7.7 (5.8,8.6) years, and the median (IQR) RHS score was 14 (10,27). SMA types were split 47% type 1, 43% type 2, and 10% type 3; 57% of patients were sitters, 33% high-functioning sitters/standers, and 10% walkers. All included participants were treated.

This initial analysis highlighted an uncertainty in the best way to define "meaningfulness" for participants. Many respondents report that any change would be meaningful due to its implication for deterioration or improvement, regardless of the impact on daily life. Functional links were provided to redirect participants toward clinically relevant considerations; however, this was variably successful. Focus groups with individuals with SMA will be conducted to identify which outcomes of change are indicators of meaningful change (i.e. modifications to care plans, increased independence.)
Meaningfulness of change was item or activity specific, rather than based on magnitude of change. A change of one or two points may have inconsistent interpretation depending on the activity and functional status, as this would have a variable impact on their daily life. These preliminary results are limited by sample size, functional variety, heavily skewed input of parents/caregivers over individuals with SMA, and challenges defining meaningfulness. Future research will aim to address these limitations through a more diverse sample and will use qualitative research to explore themes from the focus groups. This will provide specific insights into the meaningfulness of the individuals' experiences based on their age and level of function.

P190

Clinical experience in spinal muscular atrophy: Three years in a referral center in a Latin American country country

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Spinal muscular atrophy (SMA) is a severe neurogenetic disease characterized by the degeneration of alpha motor neurons in the spinal cord, causing progressive muscle weakness. It is clinically classified as types I to IV; however, the natural history of the disease has changed with the introduction of new therapies. The objective of this study is to describe the clinical experience accumulated from June 2022 to June 2025 in care at a referral center for neuromuscular diseases.

A retrospective, descriptive study was conducted at a single center in a clinic within a low- and middle-income country.

Between June 2022 and July 2025, 29 patients with SMA were treated: 11 with type I (37.9%), 8 with type II (27.6%), and 10 with type III (34.5%). Of the total, 21 (72.4%) were male and 8 (27.6%) were female. The patients' ages ranged from 3 months to 17 years. All patients had pathogenic variants in the SMN1 gene: 28 were homozygous (95%) and 1 was heterozygous with the C.724-2A>G variant. Regarding SMN2 copy number, 12 children (41.4%) had 2 copies, 16 (55.2%) had 3 copies, and 1 (3.4%) had 4 copies.
The patients came from various cities in the country, 36% from the capital. 17.2% had a family history with a confirmed or highly suggestive diagnosis of SMA.

SMA type I (n=11): Two were admitted to the outpatient clinic with tracheostomy and gastrostomy performed at another institution. Nine were hospitalized for acute respiratory failure: four, according to their families, had therapeutic efforts redirected and died; two continued with chronic respiratory failure and required tracheostomy and gastrostomy, without modified disease management. Three received Nusinersen without tracheostomy; one received a gastrostomy due to swallowing disorders and low weight. These patients showed clinical stability, improved motor milestones, and used noninvasive ventilation during sleep. Two had scoliosis, and one had not yet developed it.

SMA Type II (n=8): Two received hospital management and then continued their care at another institution. They will not continue medical follow-up. Three received Nusinersen with motor and respiratory stability; one was prescribed the drug and is awaiting initiation. One patient is receiving Risdiplam and is awaiting follow-up.
SMA Type III (n=10): Three did not continue follow-up at the institution. Six received Risdiplam and two received Nusinersen. Four patients (aged 5, 7, 9, and 13) are still walking, with stable RULM scores and lung function.

Our center treats many children with SMA, including complex cases. SMA type I patients are the most common, with a high percentage hospitalized for acute respiratory failure. A significant number of patients have been treated, altering the natural course of the disease. However, considerable challenges remain in ongoing institutional follow-up and managing severe respiratory and bulbar involvement at admission.

P192

The power of neck strength in Spinal Muscular Atrophy (SMA) patients as an outcome measure: Reliable and sensitive to change over time

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5q spinal muscular atrophy (SMA) is a progressive neuromuscular disorder which causes severe muscle weakness. This includes the weakening of axial muscles – muscles that are important for the maintenance of posture and neck movement. Monitoring neck strength could be a useful outcome measure in both non-ambulant and ambulant patients. Access to novel disease-modifying therapies (DMTs) in SMA is conditional to the demonstration of improvement or stability of their motor functions. Motor functions are traditionally monitored using various motor-function-related outcome measures. Current outcome assessments may not adequately capture changes in neck strength. Further, they may inadequately depict the benefit of the therapies, as factors such as traumatic injury, contracture and pain can significantly impact the outcome assessments.

The outcome assessments currently used to display the impact of the therapies are: WHO, ATEND, RULM and RHS/HFMSE. While other aspects are often reported by patients, their evaluation as an outcome measure has not been adequately explored. This is true for the assessment of neck strength in SMA patients. We report the feasibility, reliability, validity and change over time of the quantitative neck strength assessment, using MicroFET2 handheld dynamometer (HHD) in an adult SMA cohort.

Prospective assessment of neck strength (flexion and extension) was performed using HHD, alongside motor outcomes, health-related quality of life (HRQoL) assessments and respiratory assessment at baseline and prospectively at six-month intervals during their DMT SMA clinic visits.

Fifty-four SMA patients were included in the prospective assessment. This consisted of 44% (n=24) females and 56% (n=30) males, with a mean age of 32 years (Q1:Q3, 25,44) and consisted of 47% SMA type 2 (n=25) and 51% SMA type 3 (n=27). Fifty-three patients were on either Risdiplam or Nusinersen. HHD was well tolerated by all patients and it took less than five minutes to assess each patient.

The maximum neck flexor strength (MNFS) differed significantly between SMA type II and III, 20N and 85N respectively ($p = <0.001$). A subgroup of SMA patients showed that neck flexor strength increased over time in response to DMT ($p = 0.002$, slope = 0.36). The second subgroup demonstrated stability in neck flexor strength while receiving DMT. MNFS correlated strongly with RULM ($\rho = 0.73$), EK2 ($\rho = -0.78$) and FVC ($\rho = 0.75$) $p<0.001$.

The neck strength assessment using HHD was feasible and well tolerated and correlated strongly with motor function outcome measures in SMA. The neck strength changed from baseline, over time, to indicate treatment benefit in a subgroup of SMA. This study supports the utility of in-clinic neck strength assessment in adult SMA patients.

P194

Exploring perceptions of pilates-based exercise in adults with Spinal Muscular Atrophy (SMA)

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Spinal Muscular Atrophy (SMA) is an autosomal recessive neuromuscular condition, commonly caused by the deletion of exon 7 in the survival of motor neuron 1 (SMN1) gene. This results in a lack of survival of motor neuron protein, leading to degeneration of spinal motor neurons, progressive muscle weakness, impaired mobility, and reduced functional independence.

Advances in pharmacological therapies have improved survival and altered disease trajectories, increasing the need for adjunctive interventions that support musculoskeletal health and quality of life. The efficacy around exercise with Neuromuscular disorders is a growing and evolving topic area. Studies have investigated types of exercise, motivation and compliance of exercise however these have been focussed on aerobic and strengthening resistance training. Pilates is a mind–body exercise approach emphasising core stability, controlled movement, and postural alignment and can be adapted to the individual. Emerging evidence suggests that Pilates may enhance trunk control, respiratory function, balance, and overall physical wellbeing in populations with muscle weakness, though robust data in SMA remain limited. Pilates videos aimed at adults with neuromuscular conditions were created in 2023 and are available for all adults to access via YouTube.

The aim of this project was to explore the perceptions of Pilates exercise and self-management using online Pilates resources in adults with SMA. A questionnaire was devised and sent to all adult patients with SMA under the care of two hospitals in the United Kingdom (Sheffield Teaching Hospitals and St George's University Hospital). Data collection is ongoing until December 2025 and will be presented in more detail. Initial data shows adults with SMA reported that they believe Pilates and strengthening exercises have a positive effect on their overall health. Majority of respondents believed Pilates is suitable exercise for their condition, however a proportion of patients were unsure of the benefits of completing a Pilates programme. Additionally, barriers to participating in Pilates included fatigue, lack of time, limited access to carer support, and access to Pilates exercises.

Preliminary findings from this survey indicate adults with SMA believe Pilates-based interventions could complement existing physiotherapy programmes and be beneficial to their health. However, there is a need for delivering improved education about Pilates and strengthening exercises in this patient cohort.

P196 - FLASH TALK
Posttranslational regulation of the Survival Motor Neuron (SMN) complex
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Depletion of the survival motor neuron (SMN) protein causes malfunctions that impair human health. Recent studies suggest that posttranslational modifications (PTMs) play a crucial role in SMN function. We will focus on specific PTMs of SMN, their effects on the SMN complex, and their impact on assembly of the Sm class of uridine-rich small nuclear ribonucleoproteins (UsnRNPs).
SMN is essential for assembling Sm-class UsnRNPs as part of the macromolecular SMN complex, which includes Gemins 2–8 and the UNR-interacting protein. This complex mediates binding of seven common Sm proteins to snRNA, forming the toroidal Sm core domain of all Sm-class snRNPs. SMN binds directly to Sm proteins through symmetrically dimethylated arginine residues (sDMAs), highlighting the importance of PTMs in this process.
Although multiple PTMs within snRNP components have been reported, their roles remain unclear due to limited tools for site-specific modification. We aim to determine how PTMs on SMN and Sm proteins regulate snRNP assembly and splicing, key processes in gene expression. Understanding the structural mechanism of the SMN complex will pinpoint how specific PTMs influence SMN–Gemin2 interactions and recognition of Sm protein C-terminal sDMAs.

To overcome limitations in producing modified proteins, we employ an interdisciplinary approach combining chemical biology, biochemistry, and structural biology to enable precise modification of unexplored protein regions. Previous studies based solely on recombinant expression failed to reproduce critical PTMs involved in snRNP assembly. Our strategy has two components. First, solid-phase peptide synthesis and chemoselective ligation will generate SMN variants with defined PTMs at positions crucial for Gemin2 binding. Total chemical synthesis provides control over modification sites, allowing functional studies of snRNP assembly, structure, and protein interactions in vitro. Second, we will identify factors essential for stable SMN complex formation during splicing. Protein arginine methyltransferases, which catalyze arginine methylation, promote UsnRNP maturation by enhancing Sm protein affinity for SMN. To study this, we will use a semisynthetic approach where Sm proteins (D1/D2) fused to inteins are linked to synthetic peptides containing variable glycine–arginine repeats with sDMAs. NMR studies using segmentally isotope-labeled Sm proteins will reveal binding modes and define the minimal number of sDMA residues required for stable complex formation.
Reduced SMN levels, caused by mutation or deletion of the SMN1 gene, lead to spinal muscular atrophy (SMA), a severe neurodegenerative disease and major cause of infant mortality. Linking defective snRNP assembly to SMA underscores the need to understand how SMN-mediated splicing affects gene expression. This study will provide molecular insights into SMN function and snRNP biogenesis, supporting development of new therapeutic strategies for SMA and related disorders.

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Enhancing bulbar assessment in Spinal Muscular Atrophy: A rasch analysis of the international bulbar assessment tool (iBAT) - Pilot study

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Individuals with SMA experience progressive weakness affecting bulbar muscles and function, including deficits in swallowing, voice, and articulation. While disease-modifying therapies have proven effective, standardized and validated accessible bulbar outcomes that capture deficits across multiple domains and identify treatment effects are not currently available. We aimed to develop a low-cost, low-tech clinical outcome measure of bulbar physiology and function across all SMA phenotypes and lifespans.

The iBAT was developed through consensus and cognitive interviews, resulting in 93 items across five domains: Oral Intake Status, Oral Facial Structure and Motor Strength (20 items), Swallowing Physiology (26 items), Voice & Speech (37 items), and Fatigability (7 items). Items were scored 0–4 with higher scores indicating better function. Data were collected anonymously online via REDCap from an international cohort (August–December 2024). Rasch analysis evaluated thresholds, item/person fit, reliability, and targeting. Expert consensus was obtained through a Stanford University workshop (January 2025).

Pre-workshop analysis of 80 items revealed only 15 (19%) had ordered thresholds, primarily in voice/speech and fatigability domains. Ten items were excluded due to limited response frequency. Post-workshop refinement reduced the scale to 42 items with all items demonstrating ordered thresholds. Person fit improved (mean: 0.159 to −0.25), reliability remained good (Person Separation Index = 0.93), and item fit improved significantly (mean: 0.067 to −0.20; SD: 1.97 to 1.01). Targeting improved for middle-to-weaker populations with minimal floor effects, though ceiling effects persisted for stronger individuals. Following workshop consensus, the refined 42-item iBAT was re-administered to a new validation cohort to confirm psychometric properties and ensure reproducibility of findings.

This study demonstrates progress toward developing a clinically meaningful scale of bulbar physiology and function in SMA. The iBAT shows encouraging psychometric properties post-refinement, and it holds promise for use as both a screening tool and a validated clinical outcome measure applicable in routine clinical practice and clinical trials.

P200

The role of personalized legs orthosis in pharmacologically treated SMA 1 patient in the first year of life to promote the physiological development

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Children with spinal muscular atrophy (SMA) type 1 are achieving longer survival and new motor skills thanks to recent pharmacological advances. Despite these improvements, muscle weakness and joint instability remain, making the use of leg orthoses a crucial component of care. Custom-made orthoses, tailored to each child's growth, development, and functional status, help stabilize joints, support weak muscles, and enhance mobility, ultimately improving quality of life for both patients and families.

The design and prescription of orthoses require the expertise of orthotists with specific experience in neuromuscular diseases. The choice of materials and technical solutions must be carefully adapted to each child's comfort and functional needs. Indications for orthoses include joint alignment and stabilization, mobility enhancement, personalization to ensure optimal fit, and adaptation to different daily activities. For example, a child may need different orthoses for walking, sitting, or resting.

Several types of devices are commonly used. Ankle-foot orthoses (AFOs) may support only the ankle and foot (AFO T3), extend to the leg (AFO T4), correct equinus or supinated foot positions (positioning AFO T5), or provide knee protection with supracondylar components (functional AFO T5). Knee-ankle-foot orthoses (KAFOs), such as the Dubowitz orthosis, stabilize the knee and facilitate upright positioning, improving extension and alignment of the lower limbs. Both AFOs and KAFOs can incorporate articulated joints to allow flexion and enable targeted gait training. Hip-knee-ankle-foot orthoses (HKAFOs) extend support to the trunk, providing the stability required for standing and walking, compensating for muscle weakness, and preventing contractures and deformities.

The process of creating custom orthoses involves thorough evaluation of skeletal deformities, plaster cast fabrication, and follow-up visits for adjustments. A central aspect is the involvement and training of caregivers, including parents, healthcare professionals, and non-professional figures such as babysitters and teachers. This ensures consistent and correct use of orthoses during everyday activities, from dressing and bathing to moving at home or school. Sharing motivations and therapeutic goals with families strengthens adherence and long-term benefits.

Early prescription and regular use of orthoses can positively influence disease progression, support psychomotor development, and allow children to reach motor milestones otherwise compromised by muscle weakness. Moreover, orthoses foster greater interaction with the environment, active participation in school and social life, improved autonomy, and increased independence.

P202

Caring for the mind is caring for life - The initiative to create a booklet on mental health for people living with rare diseases

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Mental health is an essential aspect of quality of life, but still little explored in the context of rare diseases. Although there are informative booklets on clinical, nutritional and functional aspects, the psychological dimension remains neglected.

To present the experience of Viva Iris Institute, its team and people diagnosed with Spinal Muscular Atrophy, in the preparation of the booklet Caring for the Mind is Caring for Life, aimed at people with rare diseases, their families and caregivers.
The methodological process included documental research, thematic planning, face-to-face meetings between the team (n=15) and online (n=2) with adult patients with Spinal Muscular Atrophy (SMA), as well as asynchronous collaborative writing activities.
The final version of the booklet includes chapters on the impact of the diagnosis, the mourning of normality, the role of caregivers, chronic conditions and ableism as a social construct. The material was initially produced in digital format and will be printed later (2,000 copies), ensuring accessibility and wide distribution.

It is concluded that the initiative contributes to broadening the debate on mental health in the field of rare diseases, strengthening support networks, promoting social inclusion and reducing isolation. It is a strategy that combines scientific knowledge and lived experience, demonstrating the role of patient associations in the production of educational resources.

P204 - FLASH TALK

5Q SMA emergency management support tool: Collaborative construction of an emergency card

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In acute hospitalization situations, every patient is vulnerable. In the case of Spinal Muscular Atrophy (SMA), this vulnerability is even greater due to its clinical specificities. Regardless of the SMA type, emergency hospitalizations may be frequent, but the professional available in the emergency room does not always have adequate knowledge about the disease, thus applying inappropriate conduct capable of generating serious and even irreversible consequences. To reduce this risk, in the United Kingdom the "SMA Alert Cards" was cr eated by Muscular Dystrophy UK, there are records that its use contributes to adequate care and saving lives. In Brazil, until recently there was no similar initiative. During the project "SMA Patient Journey in Minas Gerais", the "SMA 5q (Types I, II and III) Emergency Card" was developed. Prepared by experts, the material brings together essential recommendations applicable to all types of SMA with guidelines for urgent situations. The process of creating the Emergency Card was collaborative, conducted in meetings with service professionals and SMA reference centers in Minas Gerais, in addition to Viva Iris Institute. The material has undergone several revisions so that the information contained is consistent and applicable to the reality of the patients. The SMA 5q (Types I, II and III) Emergency Card gathers the following data: patient identification; contact information of the reference team; functional capacity and use of medications. The card highlights critical alerts in an emergency handling and indicates priority conducts of respiratory support, anesthetic and surgical care, bulbar dysfunction and bronchoaspiration, falls and fractures, in addition to nutritional care. To deepen the guidelines, the material offers QR codes with access to complementary content, such as the SMA Practical Handling Guide, Extubation Protocol and information on the process of preparing the card itself. It is important to highlight that no emergency card replaces the decisions of the health care team, much less is it mandatory. The purpose of the card is that in an Emergency Room, for example, professionals have quick access to information about the patient's conditions for safer management. Its use can be done by any professional who is providing assistance. The first units were printed and distributed voluntarily by the project's participants, and can be freely and openly shared with those who need them.

P206 - FLASH TALK

Polysomnographic findings in children with Spinal Muscular Atrophy

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Sleep-disordered breathing is common in children with spinal muscular atrophy (SMA). The spectrum of abnormalities is broad and varies with the SMA type. Addressing sleep disturbances is an important part of personalized care, given their impact on overall health and respiratory complications associated with neuromuscular disease. Our objective was to characterize polysomnographic findings in children with SMA.

We conducted a descriptive, cross-sectional study of patients diagnosed with SMA seen between 2022 and 2025 at HOMI with a diagnosis of SMA and who had a polysomnogram (PSG) with capnography. Each study was analyzed according to the guidelines of the American Academy of Sleep Medicine.

Thirty patients with SMA were evaluated, and 22 underwent PSG. Of these, seven had SMA type 1, eight had SMA type 2, and seven had SMA type 3. Ages ranged from 2 months to 15 years, and 68% were male. Sixty-five percent of studies were conducted in the HOMI (Sleep Unit). Sleep efficiency was normal in 31% of the patients, and sleep architecture was normal in only 9% of the 18 patients with available data. REM sleep disturbances were the most common finding.
Among patients with SMA type 1, 57.1% had severe obstructive sleep apnea (OSA), 28.6% had moderate OSA, and 14.3% had no OSA. In SMA type 2, 50% had moderate OSA, 25% severe OSA, and 12.5% mild OSA. In SMA type 3, 42.9% had moderate OSA, 28.6% had severe OSA, and 28.6% had mild OSA. Three children had central apnea. Two patients received oxygen therapy during the study, so their data were not baseline. Capnography was performed in 12 patients; one (8.3%) showed hypoventilation.
At the time of the study, 71,4 of SMA1 patients, 37,5 of SMA2 patients, and 14,3% of SMA3 patients were receiving specific disease-modifying therapy. Home noninvasive ventilation during sleep was used in 42.8% of SMA1 patients, with good adherence and improvement in ventilatory mechanism. Among the remaining four patients, one did not achieve adherence (the baseline PSG was unreliable and repeated), one required tracheostomy due to worsening chronic respiratory failure, one underwent PSG during ICU hospitalization while on ventilatory support, and one had PSG upon admission before device adaptation.

Children with SMA frequently present sleep disturbances identifiable on polysomnography. The most common abnormality was moderate OSA; the prevalence of central apnea was no higher than reported in the literature. A significant proportion of patients also showed reduced sleep efficiency and altered sleep architecture for their age. Careful monitoring of sleep quality, with clinical and polysomnographic follow-up including capnography, is essential in the management of children with SMA.

P208

From Indonesian islands to the lab: Practical SMA genetic testing in resource-limited settings

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Indonesia, the world's largest archipelago, faces critical challenges in healthcare delivery due to geographical separation and unequal distribution of facilities. Molecular laboratories are largely concentrated on Island of Java, creating barriers to genetic testing in many regions. This disparity is especially significant for spinal muscular atrophy (SMA), a neuromuscular disorder most often caused by homozygous deletion of SMN1 exon 7 with or without exon 8. Early confirmation is important to treat SMA in golden period. Yet access to gold-standard assays such as MLPA or real-time PCR-RFLP is limited.

Although NAIP gene deletions, particularly in exon 5, have been described as a potential disease modifier in SMA, such deletions are considered rare in most populations compared to SMN1 deletions. Their detection usually requires comprehensive multiplex assays or sequencing approaches that are even less available outside Island of Java. Consequently, in Indonesia's current testing landscape, SMN1 exon 7/8 deletion remains the primary diagnostic target, while NAIP exon 5 analysis is often omitted or only performed in research settings. This rarity, combined with limited laboratory capacity, further widens the gap in achieving timely, comprehensive genetic profiling for SMA patients across the archipelago.

We report a 13-month-old boy from Sumatera Island who presented with progressive hypotonia, persistent head lag, and delayed gross motor milestones. Developmental screening using DDST-II revealed significant delays, while serum creatine kinase levels were within normal limits. Clinical suspicion for spinal muscular atrophy (SMA) was high; however, confirmatory testing was not available locally. Using a locally adapted bloodcard based on cellulose materials for sample collection and transport from Padang to Yogyakarta, molecular analysis was performed. Polymerase Chain Reaction–Restriction Fragment Length Polymorphism (PCR-RFLP) using DraI and DdeI enzymes confirmed a rare homozygous deletion involving SMN1 exons 5, 7, and 8.

This case highlights both a rare SMA variant and the feasibility of an innovative diagnostic approach suited to Indonesia's resource-limited, geographically fragmented healthcare system. The ability of PCR-RFLP using DraI and DdeI enzymes to detect uncommon deletions from dried blood cards underscores its utility as a cost-effective alternative.

A locally adapted blood card system combined with PCR-RFLP successfully enabled genetic confirmation of SMA in a remote setting, identifying the common SMN1 exons 7/8 deletion along with a rare NAIP exon 5 deletion. This strategy demonstrates how context-specific innovations can bridge diagnostic gaps, expanding equitable access to early SMA diagnosis across Indonesia's islands.Keywords:Spinal muscular atrophy; SMN1 exon NAIP/7/8 deletion; PCR-RFLP; blood card system; infant hypotonia; Indonesia; resource-limited settings.

P210

Evaluation a patient with SMA-type 2 - Case report

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Spinal muscular atrophy (SMA) is a common, inherited neuromuscular disease that causes hypotonia and progressive muscle weakness and wasting (atrophy).

The acquisition and maintenance of motor function is one of the key treatment goals in SMA; therefore, the assessment of motor function plays an important role in regular clinical practice and in clinical studies.

Validated and reliable scales are essential for assessing the effect of treatment on motor function in people with SMA.

Case report: Male patient. Born 1993. First functionally tested in 2021 (28 years old) Type: SMA 3B at MANU 2020 with 3 copies of the SMN 2 gene. On therapy with Evrysdi since 2021, walking up to 12 years of age. Current age 32 years old and graduated an economic school. Evaluation of the effects of therapy and kinesiotherapy with functional tests: MFM-32, RULM, SMAIS as well as measuring the range of motion in the upper and lower extremities. The patient has kinesiotherapy at home and regularly verticalizes with over-the-knee devices and help from other people.

Results: MFM-32: 53.12%; 56.25%; 53.25%; 56.25%. RULM: D32 L 24 entrance 4; R 32 L 24 entry 4; R 33 L 24 with entry 5; R 33 L27 with entry 5. SMAIS 55/58; 56/58.

Conclusion: Kinesiotherapy as a key to rehabilitation has an important role in the progression of the disease and improvement of motor function, in addition to drug therapy. Functional tests are an important tool in monitoring the progression of the disease and the only way to monitor the effects of therapy in patients with SMA.

P212

Causes of death in the Dutch SMA population (SMA types 1c–4)

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Spinal muscular atrophy (SMA) is characterised by motor neuron loss and progressive motor function decline, but SMN deficiency also affects other organs. Survival of patients with SMA type 1 is limited due to respiratory failure, but patients with SMA types 1c–4 tend to survive longer. We aim to provide updated survival estimates and causes of death among the Dutch SMA population to identify specific patterns of vulnerability in patients with SMA.

We conducted a population–based cohort study on survival and mortality in patients with symptomatic 5q–SMA types 1c–4 in the Netherlands (population 18 million). All patients were previously enrolled in the longitudinal Dutch SMA registration study. We collected data on causes of death from outpatient records from hospitals where patients were last admitted or their general practitioner.

We included 429 patients with SMA types 1c (n=42), 2a (n=131), 2b (n=60), 3a (n=111), 3b (n=71), and 4 (n=14). Estimated endpoint–free survival probability from birth (i.e., no death or >12h ventilatory support) at 50 and 70 years was 29% and 0% for SMA type 1c, 56% and 0% for SMA type 2a (sitters), 73% and 58% for SMA type 2b (sitters once able to stand), 94% and 48% for SMA type 3a, and 100% and 64% for SMA type 3b. Survival in SMA type 4 was comparable to the general population. In total, 42 patients died of the following causes: respiratory failure (n=16, 38%), sepsis (n=5, 12%), renal failure (n=3, 7%), cancer (n=2, 5%), cardiac failure (n=2, 5%), liver failure, cerebral infarction, nephrectomy secondary to recurrent pyelonephritis, unnatural (n=2, 5%), and unknown or unclear (n=9, 21%). Renal complications, including renal failure and (pyelo)nephritis, were the cause of death in 6 patients (14%) with a median age at death of 63 years (range: 43–68).

Survival is shortened in SMA type 1c–3 and respiratory failure was the expected leading cause of death. In addition, we observed renal complications as a relatively frequent cause of death in patients with SMA, underscoring the multi-system involvement of SMA.

P214

Real-world sssessment of risdiplam treatment in adult Spinal Muscular Atrophy using the goal attainment scale

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The assessment and longitudinal follow-up of adults with 5q spinal muscular atrophy (SMA) has become increasingly challenging in routine clinical practice since the introduction of diseasemodifying therapies (DMTs). Conventional outcome measures used to evaluate treatment response in adult populations present relevant limitations, particularly due to floor and ceiling effects. As a result, motor scales often fail to capture clinically meaningful changes perceived and reported bypatients.

To evaluate the usefulness of the Goal Attainment Scale light (GAS light) as a patient-reported outcome measure (PROM) for the assessment and 2-year follow-up of adults with 5q SMA treated with risdiplam in a real-world clinical setting.

We conducted a longitudinal observational study including adult patients with 5q SMA treated with risdiplam and followed annually at the neurology outpatient clinic of Hospital La Fe (Valencia,Spain). Patients were assessed using motor scales (HFMSE, RULM, 6MWT), functional scales (EK2, ALSFRS), hand strength measurement with MyoPinch (dominant hand), patient and clinician global impression of change, treatment satisfaction, and GAS light. GAS was administered at baseline prior to treatment initiation, with individualized goals defined using the SMART framework. For each goal, importance and likelihood of achievement were rated. Goals were reassessed after 1 and 2 years of treatment using the GAS light worksheet developed by King's College London.

A total of 45 patients were included (36% non-sitters, 53% sitters, 11% walkers), with a mean age of 36 years (range 15–73); 56% were women. Forty-seven percent had SMA type 2 and 53% type 3. Goal priorities differed across functional groups: non-sitters focused mainly on upper limb function and respiratory domains, sitters prioritized upper limb function, and walkers emphasized lower limb function and fatigue. Motor scales such as HFMSE and RULM showed limited sensitivity over time due to floor and ceiling effects. The 6MWT was informative only in ambulant patients. EK2 captured changes more effectively in non-sitters and sitters, whereas ALSFRS showed minimal variation. MyoPinch was useful primarily in sitters and non-sitters.

In contrast, GAS detected meaningful changes over time, with most patients achieving at least partial goal attainment, which was sustained during follow-up. Patients showing deterioration on GAS were not consistently identified by traditional motor or functional scales.

GAS light is a feasible, patient-centered, and sensitive tool for assessing treatment response in adults with SMA across all functional groups. It allows standardized longitudinal analysis while incorporating individual patient priorities and detects changes not captured by conventional scales. Appropriate goal setting using the SMART framework is essential to maximize its value in clinical follow-up.

POSTER SESSION 2

FRIDAY 13TH MARCH 2026

16.15 - 17.30

P2

Functional, fatiguability, and quality of life endpoints for spinal muscular atrophy clinical trials: Perception by health technology assessment bodies and regulators and validation status

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We explored how health technology assessment (HTA) bodies and the Food and Drug Administration (FDA) appraise the applicability of endpoints to measure muscle strength, fatigue/fatiguability, and quality of life (QoL) in clinical trials of spinal muscular atrophy (SMA). Appraisals of SMA and analogue disease treatments by the UK (National Institute for Health and Care Excellence, NICE), France (Haute Autorité de Santé, HAS), Germany (Federal Joint Committee, G-BA), and Canada's Drug Agency (CDA) were assessed to evaluate their acceptance of the Revised Hammersmith Scale (RHS), Hammersmith Functional Motor Scale Expanded (HFMSE), Revised Upper Limb Module (RULM), 6-Minute Walk Test (6MWT), 32-item Motor Function Measure (MFM-32), Pediatric Quality of Life Inventory (PedsQL), and further QoL and fatiguability endpoints. ***Ad hoc*** searches on validation and minimal clinically important difference (MCID) were performed.

Most endpoints were validated. MCIDs were identified for HFMSE (SMA type 2: 1.5; type 3: 2.4), RULM (2.9–4.3) and 6MWT (30-70m). HFMSE was considered validated (G-BA, HAS, CDA) and appropriate for advanced SMA with limited mobility (CDA). G-BA rejected the MCID provided. RULM was considered appropriate for individuals aged ≥24 (CDA) or ≥30 (HAS) months. G-BA rejected evidence on its validation and considered it less relevant than HFMSE. 6MWT was found relevant in SMA analogue diseases; however, its MCID was not accepted (G-BA), and impact of external factors could lead to bias (FDA). MFM-32 offered sufficient gradation to assess functional abilities (NICE), but longer trial duration was recommended (FDA). PedsQL was considered validated (G-BA) and correlated with mobility status (CDA). Other endpoints were not mentioned in the evaluations.
HTA and regulatory bodies generally found functional endpoints to be relevant and validated, though their perception varied by country. The applicability of functional endpoints also depended on the age and mobility status of the target population. Consideration of fatiguability and other QoL endpoints was lacking, MCIDs were not available, and validation was limited.

P4

Early speech-language intervention in an infant with SMA Type 1B: Case report

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Spinal Muscular Atrophy (SMA) type 1B is a severe neuromuscular disorder caused by SMN1 gene deletion, leading to deficiency of SMN protein essential for motor neuron survival. It manifests early with muscle weakness, dysphagia, and risk of respiratory failure, often requiring mechanical ventilation. Early speech-language intervention is crucial to promote oral functions and prepare patients for safe oral feeding. This report describes the therapeutic experience of A.W., an infant diagnosed with SMA type 1B, with two copies of SMN1 deletion, who received gene therapy in 2025. The patient began therapy at 6 months of age, in April 2025, with intensive speech-language follow-up five times per week, targeting development of orofacial and stomatognathic functions.

Speech-language intervention was structured through an Oral Sensory-Motor Stimulation protocol, including active and passive myofunctional exercises, motor point stimulation of the face, active exercises, as well as tactile-thermal, gustatory, and vibratory stimuli (Z-Vibe and therapeutic toys). The patient showed significant improvements in mobility, tonicity, and posture of speech organs, with progress in stomatognathic system functionality. Increased tolerance to intraoral stimuli and initial acceptance of small amounts of liquids were also observed. Currently, A.W. remains under mechanical ventilation but is undergoing weaning, with good prognosis for future oral feeding with adequate volume and safety.

The intensive therapeutic frequency and rehabilitation protocol proved effective, promoting significant gains in the development of orofacial structures and functions. Early and supervised intervention contributed to substantial functional progress and sustained favorable clinical conditions for future oral feeding. This case reinforces the importance of multidisciplinary follow-up in the management of children with SMA type 1B.

P6

SMA Type 1 Post-Zolgensma®: Early speech-language intervention in two cases

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Spinal Muscular Atrophy (SMA) type 1 is a severe genetic disorder associated with motor neuron degeneration and early respiratory insufficiency. Homozygous deletion of the SMN1 gene and the presence of only two SMN2 copies result in a severe clinical course. Recent advances, such as gene therapy with Onasemnogene Abeparvovec (Zolgensma®), have modified the natural history of the disease, enabling extended survival and achievement of unexpected motor milestones. However, dysphagia and feeding selectivity remain clinical challenges. This study compares two cases of children with SMA type 1, both with two SMN2 copies and treated with Zolgensma®, emphasizing the importance of early speech-language intervention to preserve oral feeding.

Both children received Zolgensma® early in disease progression and gastrostomy around two months of age. Patient C. maintained minimal oral feeding stimulation and started early speech-language rehabilitation. He evolved to full oral feeding with excellent acceptance of different consistencies and intraoral stimuli. Patient L.O., who also underwent early gastrostomy, did not receive feeding or speech-language stimulation until completing one year of age. He initially presented oral aversion, marked feeding selectivity, and episodes of dysautonomia during food introduction. With intensive therapy, L.O. achieved functional oral feeding, although with a restricted repertoire, in contrast to the broader evolution observed in patient C.

This report highlights that, even in patients treated with Zolgensma®, early speech-language intervention is crucial to preserve oral feeding and expand acceptance of food. Lack of early stimulation was associated with aversion, selectivity, and slower progress. The combination of disease-modifying therapies and early speech-language rehabilitation is essential to optimize the quality of life of children with SMA type 1.

P8

Upper limb function outcomes in Spinal Muscular Atrophy Type 1

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Early assessment of upper limb function including strength, speed, and fine motor performance are essential outcome measures to detect treatment benefit and monitor disease trajectory among patients with spinal muscular atrophy (SMA). The natural history of upper limb function after the advent of disease-modifying therapies (DMT) remains poorly characterized, especially in individuals with SMA type 1.

The aim of this study is to describe longitudinal outcomes of upper limb motor function in children with SMA type 1 treated with disease-modifying therapies in Sweden.
This is part of a longitudinal study of motor outcomes in patients with SMA treated with disease-modifying therapy in Sweden. We report outcomes of all children with SMA type 1 who received either nusinersen or risdiplam upon diagnosis. Patients were followed regularly by a specialized multidisciplinary team. From 3 years of age, upper limb strength and dexterity were assessed using the Revised Upper Limb Module (RULM), Nine-Hole Peg Test (9HPT), and grip strength measured with the E-link Jamar dynamometer.
From 3 to 8 years of age, we observed varying trajectories in upper limb motor function development (RULM), fine motor speed compared with reference values (9HPT), and grip strength (E-link Jamar dynamometer).

While clinical trials and real-world series report stabilization or improvement in upper limb motor outcomes after treatment with DMTs, a long-term evaluation of pediatric cohorts, especially in SMA type 1, with a combination of measures such as RULM, timed tests, dynamometry and patient-reported outcomes, is essential in order to define sustained functional trajectories.

P10

ThecaFlex DRx™: Implantable intrathecal catheter and subcutaneous port system for repeated intrathecal delivery of nusinersen

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Many genetic therapies, including antisense oligonucleotides such as nusinersen, require repeated intrathecal (IT) dosing via lumbar puncture (LP). LP can be challenging for individuals with Spinal muscular atrophy (SMA) that are younger, have complex spinal anatomy or require repeat anesthesia and radiation exposures. Consequently, individuals with SMA may benefit from an alternative delivery method. Currently, there are no FDA-approved IT catheter and subcutaneous port systems for nusinersen delivery to the IT space. Alcyone's investigational ThecaFlex DRx™ System is designed to facilitate IT delivery to the cerebral spinal fluid (CSF) and has received Breakthrough Device Designation in the US and CE Mark Approval in Europe. To make the device available as a nusinersen delivery method, two pivotal studies were initiated.

The safety and performance of ThecaFlex DRx™ is being evaluated in a two-stage IDE clinical trial (PIERRE, NCT05866419) delivering nusinersen to individuals with SMA. In stage 1, 10 participants were enrolled, implanted, infused with nusinersen and followed for 30 days. ThecaFlex DRx™ performed as intended, and no device-related infections or adverse events were observed. After reviewing these data, the FDA approved stage 2, which will enroll 80 patients across U.S. and Europe. Concurrently, an IND study (PIERRE-PK, NCT06555419) will co-enroll 55 PIERRE participants to evaluate nusinersen pharmacokinetics (PK). Plasma PK samples obtained following LP and ThecaFlex DRx™ administration will be compared to determine if nusinersen concentrations are equivalent between delivery methods.

ThecaFlex DRx™ may improve the IT delivery experience via subcutaneous delivery of therapies to CSF and possibly reducing the need for anesthesia and/or radiation. ThecaFlex DRx™ may benefit individuals with SMA receiving nusinersen and broader populations with neurological disorders receiving repeat IT delivery of therapeutics.

P12

Goals and therapeutic expectations of British and Italian adult SMA patients in the era of disease modifying therapies. Comparative study using goal attainment scale (GAS)

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Spinal muscular atrophy (SMA) is a progressive neurodegenerative disease, and people with SMA have varying needs, abilities, and challenges. Disease progression and treatment benefits are traditionally measured using motor function outcome measures, which may not fully reflect what matters to everyone. The Goal Attainment Scale (GAS) offers a way to capture personalized goals and patients' expectations. We investigated these aspects in adult SMA patients from two large European referral centers.

We included all adult SMA patients who completed GAS and motor outcome measures at NeMO Clinical Centre (Milan, Italy) and Sheffield Neuromuscular Unit (UK) between September 2019 and July 2025. Demographics, SMA characteristics, disease-modifying therapy status, GAS, and motor outcomes were collected at baseline and follow-up.

Data from 58 patients (n=29 per center) were analyzed. Median age was 23.35 years [20.93–40.94] in the UK and 32.66 years [24.91–48.43] in the Italian cohort. Gender distribution was 41.4% females and 58.6% males in the UK vs 48.3% females and 51.7% males in Italy. Both cohorts included mostly sitters and non-sitters, with a higher prevalence of SMA type II (53.45%). Median follow-up was shorter in the UK (8.67 months [6.30 – 12.37]) than in Italy (17.23 months [11.13 – 29.70]). The analysis did not account for the specific type of disease-modifying treatment received by patients.
In Italy, predominant patient-selected goals related to upper limb strength (35.14%) and independence in movement (21.62%). In the UK, the most reported domains were upper limb strength (33.33%) and fatigue (23.53%). Italian patients remained mostly stable (71.62%), achieving their goal in 16.22% of cases, mainly for fatigue (33.33%) and independence (25.00%). Conversely, UK patients achieved their predefined goal in 66.67% of cases, particularly in swallowing and nutrition (100.00%) and upper limb strength (73.33%).

Analysis of individual T scores showed that 60.34% of patients achieved global improvement, 29.31% remained stable, and 10.34% experienced overall worsening. When considering individual goals, post–follow-up GAS score distribution differed significantly between cohorts ($p<0.0001$). Six patients (10.34%) worsened, with more in the Italian cohort (13.79%, 4 patients) than in the UK (6.90%, 2 patients). Seventeen patients (29.31%) remained stable, mostly in Italy (51.72%, 15 patients) vs 6.90% (2 patients) in the UK. Improvement was observed in 35 patients (60.34%), predominantly in the UK (86.21%, 25 patients) compared to 34.48% (10 patients) in Italy.
We discuss factors driving these differences and highlight the utility of GAS in adult SMA. Individual therapy goals are meaningful to patients and help capture outcomes often missed by traditional motor function measures.

P15

Management of bulbar function impairment in Spinal Muscular Atrophy from a multi-disciplinary perspective in Spain

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Bulbar dysfunction is a frequent and clinically relevant complication in spinal muscular atrophy (SMA), affecting quality of life and health outcomes. Systematic assessment is limited by a lack of standardized tools, so addressing these gaps is crucial for optimizing comprehensive patient-centred-care. This study describes the current management for bulbar dysfunction in SMA patients in Spain.

A non-interventional, cross-sectional pilot study was conducted including healthcare professionals (HCPs) with expertise in SMA across Spain. Participants were invited to the study by the national SMA registry CuidAME and completed a structured electronic survey, including information regarding their demographic characteristics, and practice-related variables. A descriptive and comparative analysis was conducted. Categorical variables were analyzed with the Chi^2 test or Fisher's exact test, and quantitative variables were analyzed with the Mann-Whitney U test.

The study included 37 HCPs (62.2% female), primarily pediatric neurologists (37.8%) and neurologists (21.6%), with a mean of 9.6 years ± 5.8 of experience in SMA care. Most (86.5%) work in multidisciplinary teams at public, tertiary centers (89.2%).
HCPs placed great importance (mean 8.9/10) on bulbar function and the systemic effect of drugs for its management (mean 8.7/10). The most widely recognized bulbar domains were dysphagia (97.3%), voice and speech (89.2%), and fatigability (89.2%) which directly aligned with the main aspects evaluated: dysphagia (97.3%), voice and speech 89.2% and fatigue (83.8%)
Swallowing assessment is a common practice (94.4%), particularly in SMA types 1 and 2, performed by speech-language therapists (82.4%) and gastroenterologists (70.6%). Evaluation combines instrumental methods (videofluoroscopy: 96.8%) with non-instrumental scales (Functional Oral Intake Scale: 55.9%, Egen Klassifikation 2: 50.0%), with intervention programs available in 85.3% of these centers. Voice and speech evaluations are conducted in 59.5% of centers, with 77.3% of them offering specific interventions.

HCPs working in centers with a multidisciplinary team more frequently used instrumental assessment of bulbar function (90.6% vs. 40%; p=0.022), and videofluoroscopy (87.5% vs. 40%; p=0.037) compared to their counterparts, and were more likely to recommend bulbar rehabilitation (87.1% vs. 33.3%; p=0.013). Participation in neuromuscular clinical trials over the past five years was also higher (mean 5.2 vs. 1.7; p=0.034) for these centers Regarding professional well-being, participants predominantly showed high empathy (45.9%) and openness in evidence-based innovations (27.0%).

This study demonstrates a strong awareness and commitment among Spanish HCPs to managing bulbar function in SMA, characterized by a multidisciplinary approach and established evaluation and rehabilitation. Standardization of assessment protocols across all bulbar domains is still required.

P17

Muscle function and physical activity in children with Spinal Muscular Atrophy: A cross-sectional case-control study

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Spinal muscular atrophy (SMA) is a severe neuromuscular disease caused by mutations in the SMN1 gene. The introduction of disease-modifying therapies (DMTs) such as nusinersen (Spinraza), onasemnogene abeparvovec (Zolgensma), and risdiplam (Evrysdi) has radically improved survival, transforming SMA from a fatal disease to a chronic condition. Newborn screening, implemented in Sweden 2023, has enabled presymptomatic treatment, creating a paradigm shift. Despite these advances, many children continue to present with muscle weakness, musculoskeletal and spinal deformities, fatigue and reduced physical capacity. A deeper understanding of musculoskeletal function in SMA is essential to elucidate the underlying pathophysiology, assess how training and physical activity influence muscle size and function, and inform long-term preventive care and management strategies that may mitigate secondary complications. In the DMT era, the functional phenotypes and trajectories of muscle adaptation remain poorly understood.

To systematically evaluate muscle strength, neuromuscular control and morphology, and assess physical activity levels in pediatric patients with SMA, thereby providing an integrated profile of disease-related functional impairments and adaptive capacity.

In this cross-sectional case-control study, each included SMA patient, will be match with two age and sex-matched healthy controls. Assessments will include muscle activity (surface high-density-electromyography), muscle strength (dynamometry), muscle morphology (ultrasound) and physical activity patterns (accelerometry). In addition, joint mobility and motor function will be assessed. Outcome measures will be compared with controls and analysed across sub-groups.

Preliminary status: The project has received ethical approval. Recruitment and data collection will start in October 2025. Preliminary findings will be presented at the congress, aiming to provide novel insights into the interplay between muscle function, morphology and activity patterns in children with SMA.

This study will help clarify key determinants of muscle function in SMA in the DMT era. By linking physiology and activity to morphology and function, it aims to provide a foundation for evidence-based training interventions and preventive care strategies tailored to people living with SMA.

P19

Unbiased analysis of hippocampal and frontocortical transcriptome in a Spinal Muscular Atrophy (SMA) mouse model

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In recent years, the clinical phenotype of Spinal Muscular Atrophy (SMA) has shifted due to the availability of three effective therapies. While the predominant degeneration of motoneurons and subsequent muscular atrophy are partially prevented and the lifespan of patients is prolonged, the increasing age of patients has revealed greater involvement of peripheral organs, leading to novel symptoms and clinical needs. In addition to peripheral manifestations, potential brain involvement is of particular relevance. Emerging evidence includes reports of anatomical pathologies in the brains of SMA patients, as well as cases presenting with autism spectrum disorder-like symptoms. However, studies on patient's cognitive function in SMA remain inconsistent reporting higher, lower or normal cognitive abilities. To investigate potential brain alterations we employed the severe "Taiwanese" SMA mouse model and focused on the hippocampus, given its role in memory formation, spatial orientation and emotions, and the frontal cortex, due to its involvement in higher-order cognitive function. We analyzed mRNA expression by long-read sequencing as an untargeted method. We found several dysregulated transcripts in both brain regions at symptom onset (postnatal day 5, P5) and at a late symptomatic stage (P7). Notably, fewer dysregulated transcripts were observed in the hippocampus at P7 than P5, suggesting a potential developmental delay. Using an artificial intelligence-based prediction model, the underlying algorithms proposed several dysregulated molecular networks and changes in canonical pathway activity. Finally, predicted expressional alterations of specific targets were evaluated and confirmed at protein level. Therefore, in this study, we demonstrated hippocampal and frontocortical involvement in SMA pathology at molecular level.

P21

A comprehensive approach to investigate SMN-associated neurodevelopmental disorders: Preliminary results

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A few studies have described language and cognitive profiles of treated children with Spinal muscular atrophy type 1 (SMA1) and shown abnormalities in a proportion of them. However, the neurodevelopmental trajectories in treated SMA1 children are not fully understood, and recommendations on how to assess them to ensure early detection and interventions are lacking. This is a prospective single centre study on 73 treated SMA1 patients. Our protocol includes the following tests (at baseline and 6-monthly): Bayley Scales of Infant Development–Fourth Edition (Bayley-4), MacArthur-Bates Communicative Development Inventory (MCDI), Receptive–Expressive One-Word Picture Vocabulary Tests–Fourth Edition (R-EOWPVT-4), Social Communication Questionnaire (SCQ), Adaptive Behaviour Assessment System–Third Edition (ABAS-3), Parental Stress Scale (PSS). So far, 15/73 symptomatic patients have completed the baseline assessments, 3 SMA1a, 8 SMA1b, 4 SMA1c, mean age at first disease-modifying treatment 5.4 months (range 1-18), mean age at baseline 42.1 months (range 3-107). The following preliminary results were obtained. Bayley-4 scales (9/15, mean age at evaluation 22.5 months, range 3-43): median cognitive scaled score average (8, IQR 1-9), median receptive communication scaled score average (9, IQR 6-10), median expressive communication scaled score average (8, IQR 6-8), median fine motor scaled score average (9, IQR 5.25-10.75), median gross motor scaled score below average (1, IQR 1-1). R-EOWPVT-4 scores: median receptive standard score (7/15) average (99, IQR 82.5-100.5), median expressive standard score (8/15) average (96.5, IQR 77.5-105.5). ABAS-3 general adaptive composite standard score (15/15): borderline (75, IQR 72.5-87). MCDI - early vocabulary (n=4/15): 4/4 average score. SCQ (n=5/15): 1/5 above cut-off. In our cohort, SMA1 children treated post-symptomatically showed median cognitive score at the lower end of the average range, median receptive and expressive scores within the average range irrespective of bulbar function, and median general adaptive score in the borderline range. This ongoing data collection is expanding the knowledge on SMN-associated neurodevelopmental disorders. Longitudinal, multicentre studies are warranted to define a shared protocol and implement care recommendations.

P23 - FLASH TALK

Muscle-specific Smn depletion does not recapitulate the metabolic defects observed in spinal muscular atrophy mice

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Spinal muscular atrophy (SMA) is a detrimental childhood genetic disorder caused by reduced survival
motor neuron (SMN) protein levels. It is characterized by motor neuron degeneration and muscle wasting. However, emerging evidence demonstrates that SMA extends beyond the neuromuscular system, with significant metabolic dysfunctions affecting skeletal muscle, liver, heart, adipose tissue and pancreas. While current SMN-restoration therapies have transformed SMA prognosis and progression, metabolic defects persist even after treatment, as evidenced by our recent nutritional intervention studies. However, the multisystem organ crosstalk makes it challenging to decipher individual tissue contributions to overall metabolic dysfunction. Furthermore, the relationship between disease severity and metabolic impairment remains unclear. As skeletal muscle acts as a central regulator of inter-organ metabolic communication, we aimed to assess the correlation between muscle-specific Smn depletion and systemic metabolic defects previously observed in SMA mice.

To investigate this, we utilized previously characterized severe mice, alongside wild-type, transgenic controls and *Smn*$^{2B/-}$ whole-body Smn-depleted SMA mice as control groups. Experiments were performed in both male and female mice.

We evaluated hepatic and brown adipose tissue lipid content using Oil Red O staining and assessed glucose metabolism via glucose tolerance tests, as *Smn*$^{2B/-}$ mice have previously been reported to display aberrant lipid accumulation and glucose metabolism. Our data demonstrates that severe muscle-specific Smn-depleted mice do not exhibit the hepatic lipid accumulation observed in *Smn*$^{2B/-}$ SMA mice. Furthermore, glucose tolerance testing revealed no significant impairment in severe muscle-specific Smn-depleted mice compared to controls, contrasting with glucose intolerance in *Smn*$^{2B/-}$SMA mice.

These experiments demonstrate that muscle-specific Smn loss alone does not account for systemic metabolic defects in SMA, indicating skeletal muscle may not be the primary driver of metabolic perturbations in other tissues.

To ensure that we have not missed potential systemic effects of muscle-specific Smn depletion, we are currently performing RNA sequencing of various metabolic tissues affected in SMA and investigating serum myokine levels. These experiments will identify any tissue-specific transcriptional changes that are dependent on muscle, pinpointing primary and secondary metabolic regulatory pathways in SMA and informing the development of therapeutic strategies aimed at targeting persistent metabolic defects.

P25
Is body composition a potential biomarker for motor function in Spinal Muscular Atrophy?
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Spinal muscular atrophy (SMA) is a progressive neuromuscular disorder caused by degeneration of -motor neurons, resulting in muscle weakness and impaired swallowing, respiratory, and gastrointestinal function. Altered body composition, often not adequately reflected by BMI, has been reported in SMA, but assessment methods and their relationship to motor outcomes remain heterogeneous.

To review methods used to assess body composition in SMA and to summarize evidence on their associations with motor function.

A systematic PubMed search identified 169 publications from the last 20 years. Original studies reporting body composition in individuals with SMA, with or without analyses of motor outcomes, were included and summarized with regard to assessment technique, population, and strength of association.
Research question:

How is body composition assessed in studies of SMA?
Which associations with motor function outcomes have been examined?

Body composition in SMA has most commonly been measured using dual-energy X-ray absorptiometry (DXA), bioelectrical impedance analysis (BIA), and, in selected studies, whole-body or regional muscle MRI; anthropometry and skinfold calipers are less frequently used.
Motor function has primarily been assessed by the Hammersmith Functional Motor Scale Expanded (HFMSE), CHOP-INTEND, the Revised Upper Limb Module (RULM), and MFM-32. Across studies, lean mass and fat-free mass generally show moderate positive correlations with motor scores, particularly in ambulant children, while findings in more severely affected or adult populations are variable. MRI studies indicate that fatty muscle replacement is inversely related to motor capacity.

DXA remains the reference standard for evaluating body composition in SMA, whereas BIA offers a practical but less precise alternative. Current evidence suggests that muscle-related body composition parameters may serve as complementary biomarkers of motor function, although associations are modest and influenced by age, disease type, and treatment status. Standardized protocols and longitudinal studies are needed to clarify their prognostic value.

P27

Profile time course of motor unit regeneration and stability following administration of Smn-upregulating therapeutics

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Despite the availability of therapeutic options for SMA, impactful deficits persist in affected patients even after pre-symptomatic treatment. A hallmark of motor unit pathology in SMA involves the loss of motor neurons and disruption of neuromuscular junctions (NMJs). In this study, we employed the SmnΔ7 mouse models of SMA to profile how the motor unit recovers following administration of Smn up-regulating therapeutics.

Here, we analyzed NMJ recovery following early (PD2) administration of mono or dual Smn up-regulating therapy in the SMNΔ7 mouse model. Using the mouse cranial muscles, which allow for whole mount analysis of a group of differentially vulnerable motor units, we assessed recovery at ages P6, P12, and P18. Parameters analyzed included axon number, endplate number, and motor unit size. Additionally, we evaluated sprouting, polyinnervation, endplate size, and maturity to provide a comprehensive picture of regeneration and stability of the NMJ following early treatment with Smn upregulators in the SMNΔ7 model.

Treatment with Nusinersen significantly improved innervation of endplates at the NMJ compared to untreated littermates, even in the most vulnerable muscles. The vast majority of endplates were fully occupied by P12 and remained fully occupied at P18. However, there was an underlying loss of endplates in the most vulnerable muscles, which could mask denervation. Numbers of intramuscular axons innervating the most vulnerable muscles were also reduced from the P6 time point and in the most vulnerable muscles, continued to decline. The loss of axons coupled with stabilisation in endplate innervation gave rise to a profound increase in average motor unit size, which was progressive between P6 and P18. This work suggests that Nusinersen treatment rescues some but not all parameters of neuromuscular pathology in this mouse model of SMA, and reveals important deficits in motor unit recovery following an increase in SMN levels. Notably, motor axon loss continued after treatment leading to a progressive enlargement of the motor unit.
This study emphasizes the regenerative potential of motor neurons following Smn restoration but stresses that recovery is incomplete.

P29

Long-term persistent defects at the neuromuscular junction following pharmacological SMN upregulation in mouse models of SMA

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Spinal muscular atrophy (SMA) is a genetic neuromuscular disease characterised by SMN protein deficiency and affects neuromuscular junctions (NMJs). Although current SMN upregulating therapies have shown efficacy in preserving neuromuscular connections and prolonging survival, the long-term structural integrity at the NMJ following onset of SMN upregulating therapy is not clearly understood. Here, were report a detailed morphological study of differentially susceptible cranial muscles in 49-days-old high-dose and 63-days-old low-high dose SMN-C3 (small molecule SMN2 splicing modifier) treated SMA mice [$\boldsymbol{Smn}^{-/-}$; $SMN2^{+/+}$; $SMN\Delta7^{+/+}$ model, herein referred to as SMNΔ7] to represent early and delayed treatment-onset models of SMN upregulation, respectively. We found that at P49, high-dose treated SMNΔ7 mice showed modest but statistically significant decline in innervation status in the severely susceptible LALc and the moderately susceptible AAL muscles comparing with WT. The relatively resistant LALr was unaffected. Assessment of postsynaptic parameters revealed significant reduction in endplate number and size in the LALc but not in the other muscles. Analysis of the low-high treated SMNΔ7 mice showed even higher denervation in all tested muscles including the resistant LALr, reflecting worse pathology comparing with the high-dose treated cohort. Moreover, there was significant decrease in endplate number and size coupled with increased endplate fragmentation in all four muscles in the low-high treated cohort. Taken together, this study shows that when SMN upregulating treatment is delayed, many aspects of the NMJ cannot be recovered, even when on therapy for the same length of time.

P32

Inhibition of JNK and GSK3 signaling pathway promotes motor neurons survival and neuromuscular connectivity in both zebrafish and human Spinal Muscular Atrophy models

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Spinal muscular atrophy is one of the most common genetic motoneuron diseases in childhood. Due to mutations in the SMN1 gene, SMA is characterized by an insufficient amount of SMN (survival motor neuron) protein, resulting in denervation, skeletal muscle atrophy and premature death. In the last decade, three treatments increasing SMN protein levels have been approved by the US Food and Drug Administration and result in impressive benefits for the patients. However, several limitations still need to be addressed. Notably, these treatments are extremely costly, their long-term efficacy is not fully established and most critically, they are far less effective when administered at advanced stages of the disease. For those patients with advanced symptoms, an important step forward would be to develop therapeutic approaches targeting pathways that are independent of SMN.

To explore such SMN-independent pathways, we used a combination of human in vitro and in vivo models, including hiPSC-derived motoneurons, motoneuron–muscle co-cultures, and zebrafish models of SMA. Through these systems, we identified the multi-kinase inhibitor Kenpaullone, previously shown to exert neuroprotective effects in amyotrophic lateral sclerosis (Yang et al., 2013), as a potent modulator of pathways critical for motoneuron survival. Our findings revealed that JNK and GSK3 inhibition are particularly promising targets to preserve motoneurons. Notably, we propose Tideglusib, a selective GSK3 inhibitor with orphan drug status for myotonic dystrophy type 1, as a strong candidate for SMA that warrants further investigation.

P34

Pharmacological inhibition of microglia-mediated neuroinflammation: Effects on motor neuron deafferentation and disease progression in SMA

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Spinal muscular atrophy (SMA) is an autosomal recessive disease that represents the leading genetic cause of infant mortality. It is characterized by the degeneration of -motoneurons (MNs), which results in progressive muscular atrophy, denervation and paralysis. SMA is caused by deficient levels of survival motor neuron (SMN) protein due to homozygous deletion or inactivating mutations in ***SMN1*** gene. Neuroinflammation, involving reactive activation of both microglia and astroglia, is a common process in different neurodegenerative disorders, including MN diseases such as SMA. However, the full significance of neuroinflammation in the pathogenesis of these diseases remains unknown. In pathological conditions, microglia appear to play a major role in synapse elimination and deafferentation. Here, we analyzed the impact of microglia inhibition on SMA MN pathology.

We treated SMNΔ7 presymptomatic mice with the selective colony stimulating factor 1 receptor (CSF1R) microglial inhibitor PLX5622 (Plexxikon Inc) and performed motor behavioral tests in treated and untreated animals. Moreover, we processed tissue sections of spinal cord and analyzed neuroinflammation, autophagy, endocytosis, necroptosis phenomena and MN afferent synapses. Although PLX5622 treatment did not expand lifespan, it ameliorated motor abilities of SMNΔ7 mice. Moreover, PLX5622 inhibited both microgliosis and astrogliosis, inhibited necroptosis and prevented cholinergic synapse deafferentation of MNs in SMA.

Our findings highlight microglia as a potential therapeutic target in SMA.

P36

Regulation of the ceramide pathway as a modulator of SMN in Spinal Muscular Atrophy cellular models

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Spinal Muscular Atrophy (SMA) is a severe neurodegenerative disorder of caused primarily by homozygous deletions or mutations in the ***SMN1*** gene, leading to reduced levels of Survival Motor Neuron (SMN) protein. Clinically, SMA is characterized by the progressive degeneration of lower motoneurons, muscle weakness, and respiratory complications, remaining one of the leading genetic causes of infant mortality.
Beyond classical SMA, atypical forms have been described, including epileptic SMA due to biallelic ***ASAH1*** mutations. ***ASAH1*** encodes acid ceramidase, a lysosomal enzyme that regulates the balance between ceramide and sphingosine. Its deficiency leads to ceramide accumulation and impaired neuronal survival.
Disruption of ceramide metabolism is not unique to ASAH1-related SMA, aberrant ceramide accumulation and signalling have been implicated in Amyotrophic Lateral Sclerosis, Parkinson's disease, Alzheimer's disease, and Niemann–Pick disease, where they contribute to lysosomal and mitochondrial dysfunction, oxidative stress, and apoptosis. This link highlights the role of sphingolipid metabolism in motoneuron vulnerability.
In our work, we analysed the expression of key enzymes in the ceramide pathway in SMA cellular models: human fibroblasts, human motoneurons differentiated from iPSCs, SMNDelta7 primary motoneurons cultures. We observed significant alterations in the sphingomyelin phosphodiesterase 1 (SMPD1-encoded enzyme) protein levels in SMA motoneurons, suggesting that ceramide metabolism may be dysregulated in these cells. The modulation of these enzymes may open new opportunities for therapeutic strategies aimed at restoring lipid balance and preserving neuronal function.

P38

Effect of curcumin and its analog PGV-1 on RhoA/ROCK1 expression and Actin Cytoskeleton in Spinal Muscular Atrophy cellular model

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Spinal Muscular Atrophy (SMA) is an autosomal recessive neuromuscular disorder caused by the deficiency of the Survival of Motoneuron (SMN) protein. The resulting cellular dysfunction leads to progressive motor neuron degeneration and muscle weakness. Beyond SMN deficiency, accumulating evidence indicates that disturbances in actin cytoskeleton organization contribute to SMA pathophysiology, impairing neuronal outgrowth and synaptic function. The RhoA/ROCK signaling pathway serves as a pivotal regulator of actin filament dynamics, yet its specific involvement in SMA and its potential as a therapeutic target remain insufficiently characterized. Curcumin, a natural polyphenolic compound, and its synthetic analog Pentagamavunon-1 (PGV-1) have been reported to exert neuroprotective and cytoskeletal-modulating effects. This study aimed to evaluate the effects of curcumin and PGV-1 on RhoA/ROCK1 expression and actin cytoskeleton organization in SMA fibroblast models.

Human-derived derived SMA type I and type II cell lines were utilized as disease models, with primary fibroblasts from a healthy donor serving as controls. Following 48-hour treatments with curcumin or PGV-1, RhoA and ROCK1 protein expression levels were quantified by ELISA and validated by Western blotting. Actin cytoskeleton organization was assessed through immunofluorescence staining using phalloidin for F-actin and DAPI for nuclear counterstaining. Quantitative image analysis was performed to evaluate alterations in filament organization across experimental groups. Results: SMA fibroblasts exhibited significantly elevated RhoA and ROCK1 expression compared with healthy controls, consistent with a more disorganized actin cytoskeleton characterized by disrupted filament arrangement. Treatment with both curcumin and PGV-1 reduced the expression of RhoA and ROCK1, with PGV-1 demonstrating a more pronounced effect. Correspondingly, actin filaments in treated SMA cells displayed a more organized architecture, approaching the structural patterns observed in control fibroblasts.

This study demonstrates that curcumin and its analog PGV-1 can attenuate RhoA/ROCK1 upregulation and partially restore actin cytoskeletal organization in SMA fibroblasts. These findings highlight the potential of curcumin-derived compounds as modulators of cytoskeletal abnormalities in SMA and support further investigation into their therapeutic applications.

P40

Targeted antisense oligonucleotide treatment rescues developmental alterations in spinal muscular atrophy organoids

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Spinal muscular atrophy (SMA), caused by SMN1 gene mutations, manifests as progressive motor neuron loss and severe motor impairment, with emerging evidence suggesting that therapeutic outcomes depend critically on intervention timing during neurodevelopment. However, understanding the earliest pathogenic events in human neural tissue remains challenging due to limited access to patient samples during critical developmental windows. To address this, we utilized patient-derived spinal cord and cerebral organoids from multiple SMA type 1 iPSC lines as human neurodevelopmental models to characterize early pathogenesis and evaluate therapeutic intervention windows. Single-cell RNA sequencing revealed that SMN deficiency triggers widespread transcriptional dysregulation extending beyond motor neurons to affect neural progenitor populations and multiple neuronal subtypes, particularly impacting genes governing neuronal differentiation pathways. Multi-electrode array analysis identified consistent hyperexcitable network activity in both spinal and cerebral organoids, establishing aberrant electrophysiology as a conserved central nervous system pathology. Early-stage antisense oligonucleotide (ASO) administration successfully elevated SMN protein levels and prevented both structural abnormalities and functional deficits across diverse genetic backgrounds.

Importantly, timely intervention corrected aberrant splicing patterns in SMN1-dependent targets that are specifically enriched at neuronal differentiation regulatory nodes. Our organoid-based findings demonstrate that SMA pathogenesis involves fundamental neurodevelopmental defects affecting diverse neural populations from the earliest differentiation stages. The capacity of early therapeutic intervention to prevent—rather than merely ameliorate—these developmental abnormalities underscores the critical importance of presymptomatic treatment initiation. Human organoid models provide unprecedented access to developmental disease mechanisms and offer powerful platforms for optimizing therapeutic strategies and identifying novel intervention targets, with direct implications for newborn screening programs and precision medicine approaches in SMA and related neurodevelopmental disorders.

P42

5-year safety update: Risdiplam clinical trial program for SMA

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Risdiplam (EVRYSDI®) is a centrally and peripherally distributed, oral survival of motor neuron 2 (***SMN2***) pre-mRNA splicing modifier approved for the treatment of SMA.
The risdiplam clinical development program consists of four clinical trials:

- RAINBOWFISH (NCT03779334) in infants with presymptomatic SMA (inclusion criteria [IC]: birth–6 weeks of age at first dose)
- FIREFISH (NCT02913482) in infants with Type 1 SMA (IC: aged 1–7 months at enrolment)
- SUNFISH (NCT02908685) in patients with Types 2/3 SMA (IC: aged 2–25 years at enrolment)
- JEWELFISH (NCT03032172) in patients with SMA (IC: aged 6 months–60 years at enrolment) who previously received RG7800 (RO6885247), nusinersen (SPINRAZA®), olesoxime or onasemnogene abeparvovec (ZOLGENSMA®).

Previous analyses of 465 patients with symptomatic SMA from FIREFISH, SUNFISH and JEWELFISH (clinical cut-off dates [CCODs] 22 Nov 2022, 6 Sep 2022 and 8 Feb 2023, respectively) and 26 patients with presymptomatic SMA from RAINBOWFISH (CCOD 20 Feb 2023) showed that long-term treatment with risdiplam has a favourable safety profile. In patients with symptomatic SMA, the adverse event (AE) profiles of both the Type 1 and Types 2/3 SMA pools over the long-term remained consistent with a positive benefit–risk profile. In presymptomatic patients, the AE profile, aside from COVID-19 events, was consistent with their age.

The FIREFISH, SUNFISH, and JEWELFISH trials have been completed and the full 5-year safety data will be reported in this safety update, adding to the understanding of the long-term safety profile of risdiplam. RAINBOWFISH safety data up to 3 years into the study will also be included.

P44 - FLASH TALK

Switching DMT in SMA pediatric population: The French experience

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The SMA disease-modifying treatments (DMTs) available in France are Nusinersen (Ns), Onasemnogene abeparvovec gene therapy (GT) and Risdiplam (Rs). Data on insufficient response to DMTs are scarce. A national SMA registry was launched in 2020 in France and accounts on the last cut-off (January 2025) for 1383 patients

Analysis of phenotypic, genetic and complementary data and clinical outcomes in the pediatric SMA population enrolled at the French registry and treated by several DMTs, in order to search for patients or populations with poor response to DMTs 603 of 1025 treated patients were children (60%) and most of them were treated by Ns (406); 239 were treated by Rs and 126 by GT. Among 433 with only a DTM (244 Ns, 84 Ris, 105 GT), five SMA type1 infants died soon after treatment (3 Ns, 2 GT). Concerning the 170 patients with multiple DMTs, 139 changed from Ns to Rs after >1 year of treatment (switch Ns to Ris), 13 received GT after < 4 doses of Ns (Ns bridge to GT), 8 received Rs after GT (Rs add-on to GT) and 2 received Ns after GT (Ns add-on to GT). Most changes were prescribed due to technical difficulties in DMT administration (lumbar puncture) or due to patient/parents' choice. Poor response to a DMT was only reported in 11 children. Five of them were SMA type 1a and 1b infants (all with 2 SMN2 copies). They were initially treated by Ns with good response, but developed later in life a very progressive facial and bulbar isolated dysfunction, requiring gastrostomy. Their swallowing improved partially after switching to Rs. Moreover, eight of the children who switched from Ns to Rs re-switched again to Ns. In six of them, all sitters, re-switch was due to loss of arms strength under Rs compared to the previous effect observed with Ns. All recovered or showed stabilization of their arm strength after switching back to Ns. One patient reported recurrent vertigo episodes which disappeared after switching back to Ns. One patient switched back to Ns <6 months of treatment due to blue colored vision which persists despite the change in treatment. Ophthalmologic monitoring showed no retinal structural abnormalities.

Indication of add-on therapy after GT was validated by the national therapeutic commission given the absence of expected course after the first year of treatment with GT (arrest of improvement in oral, motor or respiratory function) but the additional DMT did not change their course significantly.

Clear loss or insufficient response to one of the three SMA therapies was very unfrequently reported in this exhaustive national real-life SMA registry. Facial and bulbar dysfunction and loss of arms strength were the earliest signs identified, respectively, in SMA1 infants and in SMA2 or SMA3 children.

P46

Adult SMA REACH: Characterisation of adult patients living with SMA at start of treatment

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Spinal Muscular Atrophy (SMA) is a rare motor neuron disease. Disease specific progression of SMA may be improved by recent disease modifying therapies (DMT) becoming available for the adult population - Nusinersen and Risdiplam are available for the UK adult population through conditional Managed Access Agreement (MAA). MAA mandates collection of Real-world data (RWD) for final drug approvals in the UK through Adult SMA REACH. Adult SMA REACH is a multi-centre longitudinal observational data collection study that collects RWD during routine clinical visit across 18 different sites in the UK. The study includes patients aged ≥16 years with genetically confirmed 5q SMA. The primary aim is to gain a comprehensive understanding of the demographic and clinical landscape of the adult SMA population at the start of treatment. Descriptive analysis was conducted for categorical and continuous variables at baseline. Mean and standard deviation (SD) were summarised for continuous variables. Categorical variables were presented as count and percentage of occurrence. Number of patients for each variable was displayed as count and percentage. The overall population included 357 SMA patients with near-equal distribution of sex. Type 3 was most common, comprising of 194 participants, followed by Type 2 with 155 participants. SMA Type 1 was rarer with only 3 participants in the total population. There was no SMA Type 4 patients included in this analysis. WHO functional status categorised patients as; 35.0% as non-sitters, 45.7% as sitters and 19.3% as walkers at baseline. The adult SMA population in the UK has a mean age at symptom onset of 3.59 years and mean age at diagnosis of 9.88 years. The adult SMA population had first access to DMT at the age of 34.5 years. Further analysis of functional assessments will be presented. This analysis provides a comprehensive baseline characterisation of adults living with SMA in the UK at the start of treatment initiation. The findings empathise the importance of early diagnosis, timely intervention, and robust RWD frameworks to advance SMA care and improve outcomes.

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Protocol of a population-based open-label cohort study to evaluate clinical efficacy of intrathecal nusinersen in older children, adolescents, and adults with SMA

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Nusinersen (Spinraza) was approved in the European Union in 2017 as the first disease modifying therapy for SMA based on results from two pivotal trials in infants and young children. Nusinersen is an antisense oligonucleotide that increases intracellular levels of functional SMN protein by modifying ***SMN2*** pre-mRNA splicing. In the Netherlands, the lack of efficacy data in children older than 12 years and adults with SMA led to the decision to reimburse nusinersen conditionally for patients starting treatment after the age of 9.5 years from 2020 to 2026. Patients had to consent to regular, protocolised assessments of motor function and quality of life that would allow the collection of follow-up data of every participant for at least 48 months. These data are to be used for the final reimbursement decision in the second half of 2026.

This is the protocol of a population-based, single-centre, open-label, observational cohort study with outcome-blinded assessments that aims to evaluate efficacy of nusinersen in patients with genetically confirmed SMA who started treatment after the age of 9.5 years.

All patients in the Netherlands with symptomatic genetically confirmed SMA, aged 9.5 years and older, will be contacted for inclusion from 2020 during a period of 2 years. We estimate that 290 patients will be eligible for screening. After inclusion, patients will receive intrathecal nusinersen according to the standard dosing schedule with a minimum duration of 48 months. Patients and their treating physicians will remain blinded to all outcome measure scores throughout the study. The primary outcome is the Hammersmith functional motor scale expanded (HFMSE) scale for patients with baseline HFMSE values ≥5 and the revised upper limb module (RULM) for patients with baseline HFSME values <5. Secondary outcomes include RULM (for patients with baseline HFMSE ≥5), HFMSE (for patients with baseline HFMSE <5), shuttle endurance tests, and patient reported outcome measures evaluating quality of life, daily life functioning, and fatigability. In addition, long-term safety and tolerability of intrathecal nusinersen will be monitored.

P50

Parenthood, family planning, and pregnancy experience and outcomes in patients with Spinal Muscular Atrophy

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The aim of our study is to expand the limited available knowledge about pregnancy and pregnancy outcomes in patients with 5q-SMA. The study is conducted in 2 parts; part 1 focuses on development and implementation of a survey with gender-specific versions on partnership, reproductive attitudes, pregnancy planning and pregnancy experiences and outcomes in Germany and Austria, and part 2 collects similar survey data from patients from multiple European countries.

To describe how patient perspectives on parenthood, reproductive attitudes, treatment-related questions, pregnancy planning, and pregnancy experience and outcomes may vary by patient demographic and clinical characteristics. We want to elucidate the frequency and nature of potential complications related to pregnancy and delivery in 5q SMA patients, neurological and psychological aspects of pregnancies and parenthood in both female and male 5q SMA patients, details about the course of pregnancy and delivery and the influence of pregnancy on SMA severity.

A project-specific questionnaire was developed to gather patients' views on parenthood, reproductive attitude, pregnancy planning and pregnancy experiences and outcomes. Patients registered in the national German-Austrian SMA patient registry (www.sma-register.de) and within the SMArtCARE registry (www.SMArtCARE.de) were invited to participate.

As part of an online survey, participants in the national German-Austrian SMA patient registry were asked to provide information on their diagnosis, partnership, family planning and, if applicable, pregnancies. The responses have been analyzed with regard to SMA type, disease-modifying therapy, gender, partnership and desire to have children.
The insights from this study will contribute to develop evidence-based recommendations for counselling SMA patients regarding pregnancy and childbirth, thereby further improving the care and quality of life for SMA patients and families.

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Description of the paediatric SMA type 1population in the Spanish CUIDAME project

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CuidAME, the Spanish national registry for Spinal Muscular Atrophy (SMA), was created in 2020 to collect real-world data after the arrival of innovative therapies. It includes all genetically confirmed SMA patients, irrespective of their treatment, with follow-up in several Spanish hospitals (target population ~1000 patients, ≥5 years). The objective is to describe the SMA Type 1 population in Spain.
Methods: Observational registry with retrospective and prospective data, including epidemiology, natural history, treatment outcomes and impact of the disease. Demographic, genetic, clinical, and functional variables were analysed descriptively. Outcomes were stratified by age at treatment initiation.

A total of 144 SMA1 subjects were registered. Of these, 141 are <18 years old (114 alive, 27 deceased). Among alive patients, 50% were male. Subtypes were classified as 14 Type 1a (12%), 56 Type 1b (49%)/ 44 Type 1c (39%). ***SMN2*** copy number was available in 113 patients: 96 had 2 ***SMN2*** copies (84%) and 17 had 3 copies (15%). All patients received a disease-modifying therapy (DMT) during follow-up: Nusinersen 50 (44%), Risdiplam 4 (4%), combination of Nusinersen-Risdiplam in 6 (5%) and Risdiplam-Nusinersen in 1, Gene therapy 25 (22%), and as an add-on treatment in 11 (10%). Stratification by age at treatment initiation showed: 1 patient treated before 15 days, 13 between 15–45 days, 26 between 46–90, 27 between 91–180, and 39 after 180 days (median 146 days). **Ventilation support** was heterogeneous: 26 without support, 74 with non-invasive, and 13 with invasive ventilation (mean age at onset of ventilation was 9 months). **Nutritional status** included 52 with external feeding (mean age at initiation was 16 months) and 60 oral. **Motor function** classification identified 20 non-sitters, 78 sitters and 11 walkers (mean age at gaining walk without support was 51months). CHOP-INTEND scores improved from a mean 22.7 at baseline to 48.5 at last visit, reflecting substantial though variable functional improvement.

CuidAME is the largest harmonized SMA registry in Spain serving as an standardized clinical lead database. It encompasses the great majority of the estimated population and is expected to increase due to the inclusion of new centers. It provides crucial data, allowing a better understanding of the new natural course of the disease, the efficacy and adverse effects of innovative therapies alongside with insights into long-term survival, functional trajectories and comparative analysis. National and international collaborations among different registries are promoted, expanding SMA knowledge.

P54

Combination disease-modifying treatment in symptomatic pediatric patients with Spinal Muscular Atrophy: Experience in Serbia

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The development of disease-modifying therapies (DMTs) for spinal muscular atrophy (SMA), together with the implementation of newborn screening programs, has led to revolutionary changes and significantly improved treatment outcomes. However, the availability of multiple approved treatment options, including nusinersen, risdiplam, and onasemnogene abeparvovec (OA), has introduced important therapeutic challenges. Increasingly, diverse strategic approaches such as switching, bridging, and add-on therapies are being applied in clinical practice.

This study aimed to present therapeutic challenges and real-world clinical experience in the selection of treatment strategies for symptomatic pediatric patients diagnosed with SMA in Serbia.

A retrospective study was conducted in five tertiary pediatric hospitals across Serbia. Data were collected for patients treated between 2018 and 2025. Children diagnosed through newborn screening were excluded from the analysis.

During the study period, a total of 92 symptomatic patients received disease-modifying therapy. As initial treatment, nusinersen was administered to 48 patients, risdiplam to 41, and OA to 3 patients. In total, 15 patients received OA at some point during their treatment course. Bridging therapy with nusinersen prior to the administration of OA was implemented in 10 patients, while risdiplam was used as a bridging agent in 2 patients. Switching from nusinersen to risdiplam was performed in 11 patients, primarily due to osteoporosis, spinal deformities and obesity that impeded intrathecal administration. In one child with SMA type 2, risdiplam was initiated as first-line therapy; however, due to poor treatment adherence, it was subsequently replaced with nusinersen. Following combined treatment with nusinersen and OA, three children received add-on therapy with risdiplam. In one of these cases, risdiplam was discontinued after one year due to a perceived lack of clinical benefit and parental preference. There were seven deaths in total: five in patients with SMA type 1 and two with SMA type 2, mostly as a result of respiratory failure associated with infections.

Long-term studies are needed to assess the efficacy and safety of both monotherapy and combination treatments in patients with SMA. A personalized therapeutic approach is essential when selecting the appropriate disease-modifying therapy. Treatment compliance, among other factors, plays a crucial role in overall management and outcomes.

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Combined Risdiplam and Onasemnogene Abeparvovec: A promising path to improve outcomes in SMA Type 1

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Spinal Muscular Atrophy (SMA) type 1 is the most severe form of SMA, with symptoms appearing within the first few months of life, significantly affecting motor function and survival. Due to the progressive nature of the disease, early diagnosis and timely initiation of treatment are crucial for improving outcomes. This case report presents the effects of a combined therapeutic approach using onasemnogene abeparvovec (OA) and risdiplam in the treatment of an infant with severe early-onset SMA type 1, and discusses potential benefits of such a strategy.

A 5-day-old infant was referred to a tertiary pediatric center due to hypotonia observed at birth. SMA type 1 was diagnosed based on clinical presentation prior to the availibality of newborn screening results. Neurological examination revealed severe generalized and axial hypotonia with reduced spontaneous movements, along with possible active movements of raising the forearms from the surface and minimal dragging of the feet on the surface. Despite severe hypotonia, the infant did not show signs of respiratory distress or swallowing difficulties. Genetic testing confirmed the absence of the SMN1 gene and the presence of two copies of the SMN2 gene. The initial CHOP INTEND score was 12/64 on day 7 of life. Given the severity of early-onset SMA type 1, risdiplam was initiated as bridging therapy before administration of OA. Prior to OA, the CHOP INTEND score had improved to 29/64. Onasemnogene abeparvovec was administered on day 27 of life, and given the significant improvement after risdiplam, risdiplam was continued as add-on therapy. Continuous improvement in motor functions was observed. By 5 months of age, the infant was able to raise hands to head level, reach for objects, briefly lift the legs off the surface, turn the head to the side, and lift the head while in a prone position. These motor improvements were reflected in a CHOP INTEND score of 47/64.

This case highlights the importance of early intervention in SMA type 1 and demonstrates the potential benefits of combining risdiplam with onasemnogene abeparvovec. The observed improvements in motor function improvements and developmental milestones, which would not have been reached in the natural course of the disease, suggest a possible synergistic therapeutic effect. Continued follow-up and further research are necessary to better understand long-term effects of combined therapies and to compare them with monotherapy. Infants with severe clinical presentations deserve access to optimal therapeutic strategies, which can significantly impact their development and quality of life.

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Early Treatment in SMA: Divergent evolution of two presymptomatic cases managed with oral Risdiplam

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The development of disease-modifying therapies has dramatically changed the diagnosis, treatment, and prognosis of spinal muscular atrophy (SMA). The three approved treatments—nusinersen, onasemnogene abeparvovec, and risdiplam—have demonstrated substantial benefits in clinical trials and real-world practice. The most significant paradigm shift in recent years has been the inclusion of SMA in newborn screening (NBS), enabling treatment at a presymptomatic stage when motor neuron involvement is minimal and normal motor development can be preserved. Nevertheless, real-world data on presymptomatic infants with two copies of SMN2 treated with oral risdiplam remain limited.

To describe the clinical and biomarker evolution of two presymptomatic infants with genetically confirmed SMA detected through NBS, both harboring two SMN2 copies without the c.859G>C modifier variant, who started risdiplam at one month of age.

Diagnosis was established by quantitative PCR with SMN1 exon-specific probes and confirmed by MLPA. Treatment was initiated with weight-adjusted oral risdiplam. Follow-up at 3, 5, 7, 9, and 12 months included motor assessment with CHOP-INTEND (0–64), neurophysiology with right ulnar compound muscle action potential (CMAP; normal > 1.5 mV), and laboratory tests (creatine phosphokinase, ultrasensitive troponin T, and plasma phosphorylated neurofilaments [pNf-L]; normal < 10 pg/mL).

Case 1: A male neonate showed normal tone and strength at baseline (CHOP-INTEND 38/64, CMAP 0.6 mV, pNf-L 936 pg/mL). After risdiplam initiation, pNf-L normalized promptly and remained stable. CHOP-INTEND reached the maximum score by 7 months and remained stable at 12 months. CMAP and troponin T normalized. Motor, respiratory, swallowing, and phonatory development were age appropriate. ***Case 2***: A female neonate presented similarly at baseline (CHOP-INTEND 38/64, CMAP 2.4 mV, pNf-L 1,637 pg/mL, troponin T 69.8 ng/L). At 6 months, an unplanned 3-week interruption of risdiplam occurred. Subsequently, CHOP-INTEND plateaued and pNf-L rose again, remaining elevated at 12 months; CMAP remained pathological and troponin T never normalized. No new motor milestones were achieved after 6 months, though respiratory and swallowing functions stayed normal.

These observations highlight several key points: (1) NBS enables presymptomatic diagnosis and immediate therapy, offering the best chance of normal development; (2) strict adherence to continuous treatment is critical, as even a short interruption of oral risdiplam may trigger measurable disease activity and halt motor progression; and (3) molecular biomarkers such as pNf-L can sensitively detect subclinical motor neuron injury and may guide therapeutic decisions, including consideration of treatment switch in case of inadequate response. Our data reinforce early treatment protocols and underline the importance of family adherence and reliable drug access to maintain the benefits of presymptomatic SMA therapy.

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Identification of new SMN-independent small molecules through an *in vivo* semi-automated drug screening platform

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The restoration of SMN protein levels is the basis of the three approved pharmacological therapies for SMA that have significantly improved patients' lives but still present some limitations. Therefore, a comprehensive approach addressing all SMA types, including both SMN-dependent and independent strategies, is essential. To this aim we have identified repurposed small molecules that work in an SMN-independent way to be combined with actual treatments by using an alternative animal model. We developed a ***C. elegans*** SMA model in which the gene ***smn-1***, the ***SMN1*** ortholog, is specifically silenced in a subset of 19 motoneurons (MNs), leading to age-dependent neurodegeneration and locomotion defects. The ***C. elegans*** SMA model phenotypes can be partially reverted to a ***wild-type*** condition when treated with candidate small neuroprotective molecules (e.g. Valproic acid), including the increase in viable motoneurons number. This finding led to the development of an innovative screening system for drug repositioning that enabled us to rapidly perform an unbiased drug screening with a semi-automated high-content imaging system counting MNs in whole living animals. With this approach we tested three FDA-approved libraries comprising 4487 compounds, and allowed the analysis of 384 compounds per week, in triplicate, on whole living animals. Thanks to this strategy we identified 19 lead compounds that counteract ***smn-1*** related neurodegeneration. Interestingly, one of the compounds, pimozide, has been recently reported effective in another SMA model of ***C. elegans***, further supporting the power of our approach. We then validated the 2 most promising compounds in a secondary screening, determining dose-response curves, the time of action and the functional effect on locomotion behavior. We also demonstrated that these 2 compounds act on different molecular pathways and their combination can further rescue the neurodegeneration defects. Finally, the protective activity of the 2 leading compounds has been confirmed in an in vitro mammalian SMA model. Our results demonstrate the high potential of our approach in identifying repurposed small molecules that suppress motor neuron degeneration by combining imaging screening and the ***C. elegans*** model. We have established a platform to deliver major progresses in defining new combinatorial treatments for preventing the neuronal death caused by ***smn-1*** loss in motoneurons.

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Early SMN-boosting improves the effects on motor function of Spinal Muscular Atrophy therapy

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Deletions or mutations in the SMN1 gene lead to insufficient SMN protein expression and trigger motor neuron degeneration in Spinal Muscular Atrophy (SMA). Yet, the presence of different copies of SMN2, a highly homologous gene, dramatically modulates the severity of the disease, which can shift from being lethal in children within 3 years of age, in the most severe form of SMA, to an invalidating condition of the adulthood. This amount of evidence emphasizes how small rises in SMN expression at the early age can have a profound impact on life expectancy, thereby prompting the development of therapeutics specifically designed to raise SMN levels. Three different agents are now clinically available. Nonetheless, they exhibit high costs, side effects, and they lead to increased SMN expression with some latency from administration. To fill this gap, we developed TAT-flSMN, a "ready-to-use" recombinant protein consisting of a cell-permeable peptidic moiety fused to the native human SMN sequence.
We characterized TAT-flSMN with an array of biophysical techniques. We then tested the protein in cell lines and iPSC-derived motor neurons, alone or in combination with a morpholino antisense oligonucleotide (ASO) designed to modify the SMN2 splicing pattern. As read-outs, we evaluated neuron-specific cellular features, such as neuritogenesis and neurite growth, as well as cell survival. Furthermore, we administered TAT-flSMN in vivo to SMN7 mice by intravenous injection, either as stand-alone therapy or in combination with intracerebroventricular administration of ASO. Animals were monitored with a range of behavioural tests and post-mortem tissues were analysed by immunohistochemistry.

In cellular models of SMA, we demonstrated that TAT-flSMN is effectively internalized into the cells. The protein can ameliorate defective neuritogenesis and neurite growth as well as reduce cell death, as a stand-alone therapy or in synergy with the ASO. Systemic administration of only 2 doses of TAT-flSMN in transgenic mice is well tolerated. In combination with the ASO, the protein anticipates its beneficial effect on motor function and leads to increased motor neuron and muscle fiber size.
Overall, we provide proof-of-principle evidence that TAT-flSMN can be a valuable add-on to the existing therapeutic portfolio for SMA.

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Final results from the JEWELFISH study: 5-year risdiplam treatment in non-treatment-naïve individuals with SMA

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Risdiplam (EVRYSDI®) is a centrally and peripherally distributed, oral survival of motor neuron 2 (***SMN2***) pre-mRNA splicing modifier that has been widely approved for the treatment of spinal muscular atrophy (SMA).
JEWELFISH (NCT03032172) was a multicentre, open-label study that assessed the safety, tolerability and pharmacokinetic (PK)–pharmacodynamic (PD) relationship of daily risdiplam in non-treatment-naïve patients with SMA (aged 6 months–60 years at enrolment) who previously received nusinersen (SPINRAZA®), onasemnogene abeparvovec (ZOLGENSMA®), olesoxime or were previously enrolled in Study BP29420 (MOONFISH) with RG7800 (RO6885247).
The enrolled population (N=174) included a broad range of ages (1–60 years), SMA types (1–3), ***SMN2*** copy numbers (2–4) and motor functions (non-sitters, sitters and walkers).
We have previously presented data after 2 years of treatment with risdiplam. The last patient enrolled in JEWELFISH completed their final study assessment after 5 years of risdiplam treatment in February 2025. Here we present the final safety, exploratory efficacy and PK-PD data from the JEWELFISH study.

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Baseline characteristics of patients with Spinal Muscular Atrophy in ACTIVENESS (BN43428) - A prospective, long-term, multi-registry post-authorisation study of Evrysdi® (risdiplam)

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Risdiplam is the only oral disease-modifying therapy (DMT) for spinal muscular atrophy (SMA). The ACTIVENESS study aims to evaluate the long-term effectiveness of risdiplam on disease progression; its design has been described previously.

The study uses pseudonymised secondary data from the SMArtCARE (Germany, Austria, Switzerland); the TREAT-NMD network registries (BNMDR [Belgium], Neuromuscular Disease Registries in Bulgaria, Georgia, and Latvia, ReaDy [Czechia/ Slovakia] and Ukrainian SMA Registry); NMiS (Sweden); and PNCR (U.S). Eligible patients have genetically confirmed 5q SMA and either initiated risdiplam in routine clinical practice (risdiplam cohort) or received no approved DMT during the eligibility period (DMT-naïve cohort). The eligibility period for risdiplam began on its commercial availability in each country; for the DMT-naïve cohort, it began when registry data met registry quality standards. Index dates were defined as risdiplam initiation for the risdiplam cohort and, for the DMT-naïve cohort, the later of first registry entry or the start of the eligibility period. The eligibility period ended in March 2025. Baseline characteristics will be presented separately by cohort and will include: age at genetic diagnosis; age at index; symptomatic status at index; ***SMN2*** copy number; comorbidities; history of respiratory support; highest motor milestone achieved at baseline; and baseline assessment results for motor function scales (e.g. CHOP-INTEND, HFMSE, RULM).

Demographic and clinical characteristics of both cohorts will provide valuable insights into the profiles of treated and untreated SMA patients in routine care. Post-baseline clinical outcomes will become available as patients continue to be followed up until the end of data collection in June 2030.

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DEVOTE Part C and ONWARD integrated results: Exploring higher doses of Nusinersen in Nusinersen-Experienced participants with Spinal Muscular Atrophy (SMA)

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DEVOTE (NCT04089566), a 3-part, Phase 2/3 trial, and ONWARD (NCT04729907), an ongoing Phase 3 open-label long-term extension study of DEVOTE, were designed to evaluate an investigational higher-dose nusinersen regimen in participants with SMA.
DEVOTE Part C (supportive; open-label) enrolled 40 children and adults (aged 4–65 years) with infantile- or later-onset SMA who transitioned to the 50/28 mg nusinersen regimen, following ≥1 year of 12/12 mg nusinersen treatment. Participants received one 50 mg loading dose four months ±14 days after their last 12 mg dose, followed by two 28 mg maintenance doses on Days 121 and 241. The primary objective of DEVOTE Part C was to assess the safety and tolerability of the higher-dose regimen.

Participant demographics were heterogeneous by design, with a wide range of baseline (BL) Hammersmith Functional Motor Scale Expanded (HFMSE) and Revised Upper Limb Module (RULM) scores. In total, 37/40 (92.5%) participants experienced adverse events (AEs); 32/40 (80%) experienced events that were at most mild or moderate in severity, while 5/40 (12.5%) experienced ≥1 severe event. The safety profile was consistent with that of 12/12 mg nusinersen. Consistent with prior 12/12 mg nusinersen treatment, BL plasma neurofilament light chain levels were within the range of neurologically healthy individuals of similar age and remained low after transitioning to 50/28 mg. Most participants experienced improvements on HFMSE, RULM, and/or Clinical Global Impression–Change (assessed by investigator/caregiver) after transitioning to 50/28 mg. At Day 302, mean (SD) increases from BL on HFMSE were +2.5 (4.22) points in ambulatory and +1.1 (3.71) points in non-ambulatory participants. Most participants showed improvements in HFMSE scores from BL. RULM scores improved by +1.8 (2.29) points in non-ambulatory and +0.6 (1.79) points in ambulatory participants. Most participants (62%) with the opportunity to improve (not at max at BL, n=26) had increased RULM scores after transitioning to 50/28 mg. These improvements were observed across phenotypes, functional status, and age.
The 50/28 mg regimen was generally well tolerated, with AEs broadly consistent with the 12/12 mg regimen. Improvements in some individuals in DEVOTE Part C were in line with those observed previously following initiation of the approved 12/12 mg regimen in treatment-naive patients, while others exceeded what would be expected in a population receiving 12/12 mg nusinersen for a median of 3.9 years. Collectively, these data support the transition of individuals from the 12/12 mg to the 50/28 mg regimen.

As of the interim data cutoff, ONWARD has enrolled 39 participants from Part C. The primary endpoint is safety and tolerability, and nusinersen 50/28 mg was generally well tolerated. Pre-dose evaluations of ONWARD Day 1 show improvement or stabilization across subgroups evaluated with HFMSE and RULM. Longer-term results, including additional endpoints will be debuted.

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STELLAR Phase 3 studies to evaluate the efficacy and safety of Salanersen in infants with Spinal Muscular Atrophy

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Salanersen (BIIB115) is an investigational, intrathecally administered antisense oligonucleotide with novel modification to the backbone and similar mechanism of action but higher potency than nusinersen in nonclinical studies, enabling the potential to maximize clinical outcomes with dosing only once yearly. Two linked Phase 3 studies will assess the efficacy and safety of salanersen in infants with spinal muscular atrophy (SMA) who initiate treatment while presymptomatic. STELLAR-1 is an open-label, single-arm study evaluating salanersen in treatment-naive, presymptomatic infants (aged ≤6 weeks) with SMA and 2 or 3 ***survival motor neuron 2*** (***SMN2***) copies. Participants will receive salanersen 80 mg annually during the 5-year study. Primary endpoints are attainment of World Health Organization motor milestones unexpected without treatment: sitting unsupported at 12-month follow-up and walking independently at 18-month follow-up for participants with 2 and 3 ***SMN2*** copies, respectively. STELLAR-2 is a randomized, double-blind, sham-controlled study evaluating salanersen in infants with SMA and 2 ***SMN2*** copies who received treatment with onasemnogene abeparvovec (OA) at ≤6 weeks of age. Participants are randomized 6 months post-OA to active treatment (salanersen 80 mg annually) or sham control. After the 12-month controlled period, participants in the sham arm will transition to active treatment. Key efficacy endpoints include plasma neurofilament light chain levels, motor function scales, and electrophysiology between groups at 12-month and 5-year follow-up. Data generated across STELLAR-1 and STELLAR-2 will provide insights on outcomes among infants who receive presymptomatic treatment with salanersen monotherapy, OA monotherapy, and OA followed by salanersen.

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Design of a Phase 2, double-blind, placebo-controlled study to assess safety, tolerability, efficacy, pharmacokinetics, and immunogenicity of ARGX-119 IV in pediatric participants with SMA: SPARKLE

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Despite available treatments, there remains a significant unmet need in spinal muscular atrophy (SMA). Neuromuscular junction (NMJ) dysfunction may contribute to the pathophysiology of SMA, including its fatigability component. Stabilizing the NMJ offers a promising therapeutic approach that complements disease-modifying therapies (DMTs). ARGX-119 is a humanized, agonistic, monoclonal antibody that specifically targets and activates muscle-specific kinase (MuSK) at the NMJ. It binds with high affinity to the Frizzled-like domain of MuSK, promoting its dimerization, phosphorylation, and activation, thereby stabilizing the NMJ. ***In vitro*** and ***in vivo*** nonclinical pharmacology studies have demonstrated the mechanism of action of ARGX-119 at the NMJ. ARGX-119, administered concomitantly with a DMT (SMN-C3, a modulator of ***SMN2*** splicing), was efficacious in an established model of symptomatic SMA in juvenile and adult mice. Therefore, ARGX-119 might significantly benefit individuals with SMA by improving NMJ function, which could reduce muscle weakness and fatigability and enhance quality of life.
SPARKLE is a phase 2, double-blind, randomized, placebo-controlled study in pediatric participants with SMA. The study aims to establish proof of concept with the age-appropriate dose and evaluate safety, tolerability, efficacy, pharmacokinetics (PK), and immunogenicity of intravenous (IV) ARGX-119. Treatment will be administered in addition to a DMT. Eligible participants will be 5–17 years old at enrollment, with a confirmed genetic diagnosis of 5q-SMA, and must have been receiving treatment with a DMT. At screening, participants must walk ≥50 m unaided in the Six-Minute Walk Test (6MWT) and have a Revised Hammersmith Scale (RHS) score >15 and <50. Primary objectives include safety, tolerability, and efficacy. Approximately 60 participants will be randomized 1:1:1 to receive age-appropriate low- or high-dose ARGX-119 IV or placebo IV during the double-blind treatment period (DBTP; 24 weeks). Dosing will occur on Days 1, 15, and 29, followed by administration every 4 weeks (Q4W). Participants who complete the 24-week DBTP period may enter the open-label, 2-year active treatment extension period, during which all participants will receive high dose ARGX-119 IV Q4W. A safety follow-up period of 20 weeks will follow the final dose. The primary efficacy endpoint is the change in RHS total score from baseline to Week 24 of the DBTP. Secondary endpoints include 6MWT distance; fatigability, assessed via performance metrics during the 6MWT and perceived fatigability using the SMA EFFORT; PK; and immunogenicity. A digital device worn on the wrist will monitor the participants' real-world physical activity. An interim analysis will be performed when all participants complete Week 12 of the DBTP. The primary analysis will follow completion or early discontinuation at Week 24. The final analysis will occur once all phases are completed or participants discontinued.

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Virtual targeted rehabilitation for patients with Spinal Muscular Atrophy: Phase 1: Proof-of-concept (VRehab-SMA project)

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With the changing disease landscape, spinal muscular atrophy (SMA) revised Standard of Care guidelines highlighted the ongoing need of a proactive physiotherapy approach. A UK national survey sent to people living with SMA and caregivers (2022), access to physiotherapy was ranked as limited, with 64% seeing a physiotherapist once a year. The ongoing ACE SMA study (NCT06419322) collected positive feedback from people living with SMA and their caregivers towards regular hands-on physiotherapy with the use of commercially available rehabilitation devices at home for exercising. Indeed, at 6 months, 90% (14/14 participants) were likely to recommend the hands-on physiotherapy and device use, and all were satisfied with the care compared to NHS services (unpublished data). Yet, these devices require transfers from wheelchairs and consecutively the assistance of a caregiver as well as sometimes challenging positioning.
To further support people living with SMA in their regular exercise program, the VRehab SMA study team; clinicians (STRONG) and engineers from the University of Oxford, seek to develop a virtual rehabilitation technology that provides individualized exercise programs for people living with SMA without the need for transfers, thereby enabling safe and independent use. This technology aims to provide an at-home rehabilitation solution, enabling parents to facilitate daily exercises in a more accessible and enjoyable manner. It would constitute the first of its kind in the SMA field, involving the integration of augmented electromyography signals and soft robotic haptic devices into a gamified virtual reality environment. By increasing the frequency and quality of exercise interventions at home, this technology has the potential to significantly addressing the critical unmet need for consistent rehabilitation and exercising. This technology will also serve as clinical outcome measure as continuous home-based assessment of weaker and less functional population and decrease the burden of hospital-based assessments.
The VRehab SMA study is divided into several phases to ensure a robust development of the technology:
2024: Development of technology
2025/2026: Phase 1: Proof-of-concept: Improvement of technology
Phase 1.1: Testing on healthy volunteers: September 2025
Phase 1.2: Testing on a small number of people living with SMA: planned in February - June 2026
2026: Phase 2: Testing in controlled environment: planned start by Q4 2026
2027/2028: Phase 3: Testing in uncontrolled environment

We aim to present the preliminary results of Phase 1.1 which investigated the safety and experience collected in 10 healthy adult volunteers. Primary outcome measure was to evaluate the safety measuring the adverse events during and one week post visit. Secondary outcome measure was to assess the experience of each participant conducted using a 5-point Likert scale satisfaction questionnaire. These results constitute the base of this multiphase development project.

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A cross-sectional study to evaluate the clinical characteristics and nutritional status of children with Spinal Muscular Atrophy

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Spinal muscular atrophy (SMA) is a chronic neuromuscular disease characterized by spinal motor neuron degeneration. Researches revealed that the prevalence of malnutrition is quite high although it varies according to the type of SMA. nutritional goals. This study was aimed to assess clinical characteristics feeding features and nutritional status of pediatric outpatients with SMA.
In a single visit, information was gathered on the patient's anthropometrics, the results of the nutritional status assessment , birthdate, age at SMA diagnosis, etiology and type of SMA.

Anthropometric measurements obtained Malnutrition was defined according to data of percentiles of Gomez and Waterlow Classifications using CDC standard growth charts.
The study was conducted with 24 children with SMA. The mean age of the patients was 90.67± 50.72 months (5-192). Eleven children were diagnosed as SMA type 1 thus representing the most severe form of SMA.
The means of Hammersmith Functional Motor Scale (HFMS) and Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) were 36.18 ±17.08 and 37.85 ±21.21 respectively. More than half of study group were able to self-feed (54.2%). The percutaneous endoscopic gastrostomy (PEG) was the route of feeding in 33% of cases. The result of mid-upper arm circumference band measurements revealed that 14 (58.3%) children had malnutrition and one patient was overweight.
In general, Gomez classification (WFA) revealed that malnutrition was evident in 58.3% of children with SMA based on CDC growth charts. According to the Waterlow (stunting) classification of HFA based on CDC growth charts, 54.1% of patients were chronic malnourished.

This study presents clinical features and nutritional status of children diagnosed with spinal muscular atrophy (SMA), emphasizing the high prevalence of malnutrition and the factors influencing nutritional health in this population. According to Gomez classification based on weight-for-age (WFA), 58.3% of the patients were malnourished. Similarly, the Waterlow classification using height-for-age (HFA) indicated chronic malnutrition in 54.1% of the cohort. The consistency across these different methods underlines the importance and urgency of addressing malnutrition in children with SMA. The malnutrition rates were most prominent in **SMA type 1,** the most severe phenotype, suggesting a direct correlation between the degree of neuromuscular impairment and nutritional status.
MUAC (mid-upper arm circumference) z-score analysis also identified 58.3% of the children as malnourished.

A previous study with type 1 and type 2 cases, revealing that the mean weight was significantly lower in SMA patients than healthy controls, while supine length was more variable. They also present here a set of disease-specific percentile curves of BW, SL, and BMI-for-age for girls and boys with SMA1 and SMA 2. However, these specific curves are not approved by ESPGAN yet.

During follow up SMA patients should be monitored in term of nutritional status. A retrospective study done with sixty cases reported that weight z scores have decreased in %23 of patients. This ratio was % 47 in BMI.

Feeding and swallowing problems are one of the most important complications of SMA. Dysphagia in SMA type 1 may also lead to other problems such as poor weight gain, discomfort and risk of aspiration pneumonia. Choking and sweating during feeding were reported as %91 and %55 in SMA patients respectively. It has been reported that 72% of patients had to interrupt feeding due to this coughing attack and sweating. As a result, duration of feeding prolongs. In our study, half of participants reported that duration was more than 15 minutes.
Standard anthropometric measurements can be challenging in children with SMA due to spinal deformities. In our study, MUAC was highly consistent with traditional malnutrition classification systems and offered significant advantages in terms of usability, age independence, and minimal technical requirements.
In recent years, dramatic and hopeful developments occurred in therapy of SMA. Although studies reported improvement in dysphagia, it is not dramatic as motor functions. When considering nusinersen, which is the commonly used drug, studies have suggested that the drug may have less effect on the brainstem than on other parts of the spinal cord.

This study has several limitations. The small sample size and single-center design may limit the generalizability of the findings. Moreover, the cross-sectional nature of the study precludes analysis of longitudinal changes in nutritional status or the effects of interventions over time. Nevertheless, the use of multiple anthropometric indicators and validated classification systems strengthens the credibility of the findings.
In conclusion,
A multidisciplinary approach is essential. Early swallowing evaluations and timely transition to enteral feeding in at-risk children can prevent further nutritional decline.

P80

Newborn screening for SMA in Serbia: Expert committee–led personalized treatment and real-world challenges after two years of implementation

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Serbia introduced genetic newborn screening for spinal muscular atrophy (SMA) in 2022, with nationwide implementation beginning in September 2023. The program is centralized at the Faculty of Biology, University of Belgrade, a center of SMA diagnostics and research since 1997. Within its first two years (September 2023–September 2025), 120,470 newborns were screened, leading to the identification of 19 infants with SMA. Seventeen of these infants received treatment, most before six weeks of age. Among them, 6 had 2 ***SMN2*** copies, 7 had 3 copies, 4 had 4 copies, and 2 had 5 copies.

A distinctive feature of the Serbian model is the establishment of a multidisciplinary National Expert SMA Committee, comprising pediatricians, neurologists, a patient representative, and a molecular biologist. The Committee evaluates each confirmed case, integrating molecular, biochemical, and clinical findings to guide treatment decisions. ***SMN2*** copy number serves as a central but not exclusive parameter, considered along with therapy-specific contraindications, family compliance, and home environment. This structured approach ensures that each infant receives a fully personalized treatment plan that balances medical evidence with practical realities. It also allows limited financial resources to be used rationally, while meeting the needs of every newborn diagnosed with SMA.

Implementation of the nationwide newborn screening has not been without challenges, which can be grouped into pre-analytical and post-analytical issues. Pre-analytical challenges include gaps in sample traceability before arrival at the central laboratory, creating the potential for undetected sample loss. Post-analytical challenges are multiple: parents may refuse to perform clinical evaluations or confirmatory testing – one case of maternal neglect led to the inability to confirm a positive screening result and unsuccessful attempts by social services and police to reach the family, ultimately delaying diagnosis and treatment. Bridging treatment between therapies is not permitted and is emerging as an important challenge. In several cases, parents reported that they had independently purchased and administered risdiplam prior to planned gene therapy. Such situation may complicate interpretation of potential biomarker levels (e.g. neurofilaments) and assessments of treatment efficacy, potentially affecting both clinical decision-making and research outcomes. Switching therapies once initiated is not permitted also, and remains a highly complex issue that further underscores the importance of careful initial decision-making by the Committee.

These combined advantages and challenges demonstrate that the effectiveness of newborn screening extends beyond laboratory excellence and expert decision-making. Success depends equally on efficient logistical systems, proactive family engagement, and robust social support structures to ensure that every diagnosed child receives timely and appropriate care.

P82

Feasibility and diagnostic yield of a pilot SMA newborn screening program in Israel: High parental acceptance and first national incidence estimate

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Spinal muscular atrophy (SMA) is a severe neuromuscular disorder for which pre-symptomatic treatment dramatically improves survival and motor outcomes. Universal newborn screening (NBS) enables early diagnosis but has not been implemented nationally in Israel. Existing prenatal carrier screening captures only a portion of affected births. We conducted the first pilot SMA NBS program at a tertiary maternity hospital in Israel to evaluate feasibility, parental acceptance, workflow integration, diagnostic performance, and incidence.

Between July 2024 and February 2025, newborns delivered at Lis Maternity Hospital were offered SMA NBS integrated into routine dried blood spot (DBS) collection. Parents were approached postnatally for informed consent prior to routine metabolic screening. Initial screening used a high-throughput real-time PCR assay targeting SMN1 exon 7. Newborns with positive screens underwent confirmatory testing using multiplex ligation-dependent probe amplification (MLPA) to determine SMN1 and SMN2 copy numbers. Turnaround times, consent rates, screening and confirmatory results, and technical challenges were analyzed.

(Novel Data): Of 6,913 parents approached, 95% consented to SMA NBS, with an average recruitment rate of 42 consents per day. Integration into the standard postpartum workflow did not disrupt routine care. Among parents who declined participation, the most common concerns included anxiety regarding genetic testing, uncertainty about the clinical implications of positive results, and a perception that screening was unnecessary in asymptomatic newborns. Laboratory testing was performed biweekly due to manpower limits, resulting in turnaround times of 2–6 weeks. Four newborns screened positive on initial PCR; MLPA confirmed one true-positive case with homozygous SMN1 deletion and four SMN2 copies. The remaining three were false positives caused by allele dropout due to primer-binding site interference—a known but still underreported technical challenge in high-throughput screening. No false negatives were identified during the study period. The observed incidence in this cohort was approximately 1:7,000 live births (14/100,000), representing the first prospective incidence estimate of SMA in an Israeli newborn cohort.

This pilot demonstrates that SMA NBS is feasible in Israel with exceptionally high parental acceptance across diverse populations. A two-tier testing strategy minimized false positives and ensured diagnostic accuracy. The study provides the first reported incidence estimate in Israel and identifies key operational challenges relevant to national implementation, including laboratory throughput and confirmatory pathways. These novel data support the integration of SMA into Israel's national newborn screening panel to enable earlier diagnosis and presymptomatic treatment, with implications for other regions currently evaluating SMA NBS.

P84

Optimization of diagnostic, treatment, and prevention of Spinal Muscular Atrophy in Uzbekistan: A review (2021-2025)

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Spinal muscular atrophy (SMA) is a severe autosomal recessive neuromuscular disorder that represents a major challenge for pediatric healthcare systems worldwide. Uzbekistan, with a population of approximately 38 million and an annual birth rate of nearly 1 million newborns, is estimated to have between 93 and 155 new SMA cases annually. Since 2021, systematic national efforts have been undertaken to establish early diagnosis, expand access to pathogenetic therapy, and ensure long-term rehabilitation and social adaptation for children with SMA.

A unified national SMA registry was established, integrating clinical, genetic, and functional data. Key steps included the introduction of confirmatory MLPA diagnostics, training of multidisciplinary teams, pilot treatment programs with risdiplam subsequently expanded nationwide, legislative support through Presidential Decree No. 217 (2022) ensuring free medical and social care, and the development of patient organizations ("SMA Umid") with international collaborations.

As of August 2025, the registry included 284 patients with SMA (46% type I, 35% type II, 19% type III), of whom 215 (75.7%) received pathogenetic therapy. Risdiplam procurement increased more than 20-fold between 2021 and 2024. The number of patients receiving targeted therapy rose from 11 in 2021 to 182 in 2025. Early diagnosis improved substantially: in 2021–2023, 42.5% of type I SMA cases were diagnosed before 6 months of age, compared with 59.6% in 2024–2025. Access to early therapy also increased: in 2021–2023, 13.2% of patients with type I SMA began treatment before 6 months, versus 36% in 2024–2025. Survival outcomes improved as well: among type I SMA patients receiving targeted therapy, the survival rate was 65.2%, with 74.5% living beyond 2 years of age. Prenatal viability testing in high-risk families revealed 0 copies of exon 7 of SMN1 in 25% of cases, 1 copy in 54.4%, and 2 copies in 20.1%.

Uzbekistan has achieved substantial progress in SMA care through coordinated state programs, registry development, and expanded access to risdiplam. Future priorities include the establishment of state genetic laboratories, implementation of neonatal SMA screening, expansion of presymptomatic therapy and carrier testing programs, development of regional rehabilitation centers, and broader access to gene and combination therapies. These results demonstrate that structured healthcare policies in lower-middle-income countries can significantly improve outcomes for rare genetic disorders such as SMA, positioning Uzbekistan as a potential model for similar healthcare systems

P86 - FLASH TALK

Management and aspects of pregnancy of SMA on Nusinersen treatment - Case series

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Since 2016, the first disease-modifying therapy, nusinersen, has been approved and is now available for all SMA subtypes. The introduction of disease-modifying treatments has led to the emergence of new patient phenotypes that differ from the classic SMA types, as well as novel clinical challenges for both healthcare providers and patients. One of these challenges is the management of pregnancy in women receiving ongoing therapy.

We report two cases of female patients with SMA type 3 who continued nusinersen treatment during pregnancy and lactation. Both pregnancies were closely monitored, focusing on potential changes in SMA-related symptoms through regular motor performance assessments and on pregnancy outcomes. The treatment regimen was maintained throughout pregnancy in both cases, with minor adjustments according to individual preferences.

To date, only limited information is available on the safety of innovative SMA therapies during pregnancy. In both cases presented here, no adverse maternal or fetal outcomes were observed, and both infants were healthy during a one-year follow-up. The decision to continue pharmacotherapy during pregnancy should always be based on a careful, individualized risk–benefit assessment, taking into account the patient's best interests through shared decision-making between the patient and the clinical team.

P88 - FLASH TALK

Anesthetic risks during intrathecal nusinersen admission in children with Spinal Muscular Atrophy Type 1

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Spinal Muscular Atrophy (SMA) causes progressive weakness of the upper airway and respiratory muscles, leading to recurrent respiratory infections, declining lung function, and increased mortality. Nusinersen, an intrathecally administered ***SMN***-augmenting therapy, improves motor function and survival in children with SMA. As per protocol, treatment of children up to 12 years in our center is performed under general anesthesia. Severe forms such as type 1 are complicated by respiratory and bulbar symptoms, including impaired airway clearance, hypoventilation, aspiration and restricted mouth opening, which may complicate the use of general anesthesia. Few studies have evaluated the anesthetic risks in children with SMA undergoing general anesthesia for intrathecal nusinersen administration. This study aims to evaluate the peri- and post anesthetic complications associated with nusinersen administration in children with SMA type 1.

Methods: We performed a nationwide retrospective cohort study in children with spinal muscular atrophy type 1 who received nusinersen under general anesthesia between May 2017 and May 2025. The primary outcome was the occurrence of respiratory complications. Secondary outcomes included all non-respiratory complications observed.

Results: We included 31 patients (n=9 SMA 1b, n=22 SMA 1c), who underwent a total of 557 procedures for intrathecal nusinersen administration under general anesthesia. Respiratory complications occurred in 102 (18.3%) procedures in 25 patients (80.6%) and included compromised airway clearance with sputum retention (n=63), increased ventilatory support (n=4), desaturations not requiring oxygen supplementation (n=21), and desaturations requiring oxygen supplementation (n=51). One patient required a post-procedural intubation and admission to the pediatric intensive care unit. Unplanned hospitalization was required after 10 (1.8%) procedures. We did not identify procedures resulting in resuscitations or death.

Conclusion: Administration of intrathecally under general anesthesia carries significant risks in children with SMA type 1. Respiratory complications are common, though usually mild. Serious adverse events with readmission or intubation were rare. These findings highlight the importance of counseling healthcare professionals and parents regarding potential anesthetic risks. For patients with severe respiratory and bulbar involvement, alternative treatment should be considered. At present we are analyzing risks of general anesthesia in patients with SMA type 2 and 3a, as well as continuous perioperative data, with a focus on desaturation during general anesthesia.

P90

International evidence-based consensus on the management of gastrointestinal adverse events related to the use of risdiplam in patients with SMA

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The selective survival of motor neuron-2 mRNA-splicing modifier, risdiplam, is the first oral treatment approved in Europe and the USA for the treatment of people with spinal muscular atrophy (SMA). Across pivotal trials, risdiplam has been shown to improve motor function in infants with presymptomatic SMA, as well as children and adults with Types 1–3 SMA for up to 5 years. Additionally, risdiplam is well-tolerated, with the most frequently reported adverse events (AEs; in ≥ 5% of patients) including fever, diarrhoea and rash. Although trial data have shown that treatment-related diarrhoea does not lead to discontinuation of risdiplam, in the absence of best-practice recommendations, instances of pausing risdiplam treatment to resolve diarrhoea have been reported in clinical practice. Owing to the treatment benefit offered by risdiplam, there is a need to consider recommendations for the management of potential gastrointestinal (GI) AEs experienced by people with SMA treated with risdiplam.

To address this need, an international panel comprising neurologists, gastroenterologists and patient experts (N = 14) were recruited to participate in a modified Delphi consensus process. Following a targeted review of published literature reporting clinical and real-world outcomes relating to GI AEs experienced by people with SMA treated with risdiplam, the Delphi panel steering committee (n = 5, including a patient expert and two non-voting co-Chairs) gathered to discuss the evidence and their experiences. The outcomes of these discussions, supported by the published evidence identified, informed the generation of 19 draft consensus statements concerning the clinical management approaches to GI AEs related to the use of risdiplam. The statements were taken through up to three rounds of voting, during which panel members voted anonymously on each statement using a 6-point Likert scale. A non-voting patient advisory panel (N = 6; including people with SMA and caregivers of children with SMA) reviewed each statement and provided anonymised feedback to the patient expert steering committee member for consideration. Statements that failed to reach a pre-defined consensus threshold (≥ 75% agreement) were revised based on clinical and patient expert feedback and carried through to the next round of voting. Statements were considered final if they meet the pre-defined consensus threshold in any voting round.

Here we present the finalised consensus statements. It is hoped that the statements generated using this modified Delphi consensus method will inform clinical decision-making related to the management of treatment-related GI AEs in patients with SMA who receive risdiplam.

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Spinal cord stimulation targets circuit dysfunction to improve upper-limb function in non-ambulatory adults with SMA

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Pre-clinical models indicate that a hallmark feature of SMA is not only MN death but also MN dysfunction due to decreased proprioceptive inputs, leading to hyperexcitable MNs with prolonged refractory periods and paradoxically reduced firing rate. As such, along with available therapies that prevent MN death, targeting spinal sensorimotor circuitry to improve circuit and consequently MN function is necessary to treat motor deficits that persist despite SMN restoration. Since spinal cord stimulation (SCS) activates sensory afferents, we hypothesized that increased input to MNs via SCS could address this circuit dysfunction. Indeed, we previously showed in three ambulatory adults with SMA that SCS improves strength, gait quality, and endurance in only 4 weeks. Here we report a follow-up trial (STUDY21080158) building on our prior work which tested cervical SCS in three non-ambulatory adults with SMA in the absence of exercise to explore improvement of function of the upper limb. We temporarily implanted (29 days) epidural leads over the cervical spinal cord of three non-ambulatory participants (SMA04: male, 56 y/o baseline RULM: 8/37, SMA05: female, 21 y/o, baseline RULM: 20/37, SMA06: male, 60 y/o, baseline RULM: 34/37). To isolate stimulation effects from exercise, SCS was delivered unilaterally, using the contralateral arm as an internal control. Participants received 2 hours/day of stimulation during strength testing and 3D reaching tasks. Despite differences in age and disease severity, all participants showed increased strength (grip: up to +184%, elbow ext: up to +190%) and improved reaching kinematics, including increased smoothness, range of motion, and movement velocity. Gains were consistently higher in the stimulated arm, indicating that exercise alone is unlikely to explain the improvements. Importantly, over the four-week study period, participants also reported meaningful functional gains in daily life, including being able to unbutton a shirt, independently open doors and open the car's gas tank door. Together, these results suggest that cervical SCS can complement SMN-based therapies by targeting spinal circuit dysfunction to improve upper-limb motor function in SMA.

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SMA Care UK: Ensuring the best respiratory care for individuals with SMA across the UK

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The 2018 international care recommendations for spinal muscular atrophy (SMA) were published prior to the availability of disease-modifying treatments (DMTs), which have significantly altered the clinical course, phenotype, and prognosis of the condition. These guidelines were largely focused on paediatric populations and were based on motor milestones with recommendations for walkers, sitters and non-sitters.

SMA Care UK is a collaborative initiative involving healthcare professionals, people living with SMA and other stakeholders. Its goal is to update evidence-based standards of care and harmonise best practice in response to the priorities of the SMA community and the changing landscape of SMA. A working group of health care professionals and patient experts was convened to address respiratory care, including respiratory, neuromuscular and intensive care clinicians, specialist physiotherapists and nurses with expertise in managing both children and adults with SMA.

The working group (WG) undertook a comprehensive review of current recommendations. Drawing on emerging evidence, evolving clinical practice and areas of unmet need, draft guidance covering the assessment, management and treatment of respiratory complications, including emergency and peri-operative care, across the paediatric-to-adult continuum has been developed. The updated guidance is based on individual symptoms and signs rather than motor function in and of itself and is targeted at health care professionals who are not experts in respiratory care in SMA for example those working in emergency departments, general paediatric and medical clinics.

The draft guidance has undergone a first round of consultation through the SMA REACH and UK respiratory networks. Feedback is being addressed and a second round of consultation will follow to achieve consensus. The group is working with the British Thoracic Society, NICE and wider SMA REACH clinical networks to ensure that the guidance is endorsed and published.

In parallel, family friendly guidance is being produced aimed at both children and adults. Gaps in evidence have been identified and the WG are considering strategies to address these. SMA Care UK is committed to collaborating with international networks to ensure the guidance remains aligned with global best practice.

P99

SMA Care UK: Ensuring the best transition from paediatric to adult care for individuals with SMA across the UK

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The 2018 international care recommendations for spinal muscular atrophy (SMA) were published prior to the availability of disease-modifying therapies (DMTs), which have significantly altered the clinical course, phenotype and prognosis of the condition. These guidelines, intended as a global minimum standard of care, were largely focused on paediatric populations and did not account for the novel and evolving phenotypes now observed.

SMA Care UK is a collaborative initiative involving healthcare professionals, people living with SMA and other stakeholders. Its goal is to update evidence-based standards of care and harmonise best practice in response to the priorities of the SMA community and the changing landscape of the condition.

While the 2018 standards provided a foundation for SMA care, they focused primarily on children and offered limited guidance on adult needs or the transition from paediatric to adult services. With longer survival and broader phenotypes in the era of DMTs, structured, individualised transition planning has become a critical component of long-term care. Without a formative transition process, many young people are at risk of disengaging from health care altogether, and some who did not engage with adult services are now struggling years later. This highlights the need for close communication and cooperation between paediatric and adult teams to safeguard continuity of care. Effective transition requires multidisciplinary input, ongoing assessment of functional and medical needs, and support for self-management and quality of life across adolescence and adulthood. Evidence indicates that fragmented transition can compromise access to care and functional support, underscoring the need for formal guidance to ensure systematic, personalised pathways across the lifespan.

In response, a multidisciplinary team, including individuals living with SMA and expert adult and paediatric healthcare professionals such as neurologists, physiotherapists, specialist care advisors, specialist nurses, occupational therapists and social workers, has undertaken a comprehensive review of current evidence and practice for transition care. This process included surveys of centres and patients to better understand existing experiences. The team will be developing draft guidance to support structured, personalised transition pathways and continuity of care from paediatric to adult services. They are working with relevant professional bodies and NICE to ensure the guidance is endorsed and published for clinical implementation.

In parallel, gaps in evidence have been identified, with strategies being developed to address these, including future evidence-gathering and collaboration with international networks to ensure that the guidance remains aligned with global best practice.

P101

Exploring the lived experience of young adults living with Spinal Muscular Atrophy (SMA) transitioning from paediatric to adult services in the United Kingdom

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To explore the lived experience of young adults living with Spinal Muscular Atrophy (SMA) transitioning from paediatric to adult services in the United Kingdom.

There is a paucity of literature describing the transition from paediatric to adult services for young adults living with SMA in the United Kingdom. Improved access to Disease Modifying Therapies is increasing the number of young adults transitioning to adult services. Research conducted in the American population suggest improved communication between teams and access to support resources related to building independence during this stage of life are desired. In addition, it is suggested that the mental health burden is increased during transition, and that young adults would benefit from increased peer support at this time.
The adult SMA Service at St George's Hospital in Southwest London is looking to expand the support offered to young adults during their transition from paediatric to adult care. The aim of this research is to better understand the needs of the young adults living in the region with SMA to improve the care and support provided. Further, co-producing resource materials and establishing a means for peer support will be explored with the young adults.

A mixed-methods approach with purposive sampling will be used. Young adults between the ages of 17 – 25 years will be recruited through the hospital database. An online survey will be conducted to collect demographic data. Open-ended questions will collect information about aspects of transition that worked well, and how things could be improved. Key priorities of young adults will be highlighted. A small focus group of 3-6 young adults will be conducted to gain further insight into the transition process.

Descriptive statistics will be used to collate demographic detail. Qualitative data will be analysed through Reflexive Thematic Analysis. Study is ongoing.

P103

Physiotherapy management of jaw contracture within the UK Adult SMA REACH Network: A service evaluation to establish current practice and inform future standards of care

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With thanks to the Adult SMA Reach Physiotherapy Network

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The success of novel pharmacological treatments is extending life expectancy in Spinal Muscular Atrophy (SMA). As a result, the clinical significance of bulbar weakness and related secondary complications such as contractures of the jaw, are becoming more widely recognised in adults living with SMA.

Progressive weakness and degeneration of bulbar muscles inevitably cause mechanical impairment of oral function. Loss of mobility at the jaw has long been associated with difficulty articulating speech, poor oral hygiene and challenges accessing dental care for those with SMA. Significant clinical risk has also been acknowledged, including complicated endotracheal intubation and limited nutritional intake leading to malnourishment. Despite this, the existing Standards of Care offer minimal guidance for assessment or management of jaw weakness or restriction.

This service evaluation aims to establish current practice in this area within the United Kingdom (UK) Adult SMA REACH network of physiotherapists. Initial audit demonstrated inequitable access to jaw assessment by a physiotherapist, with jaw range of motion measurements recorded in less than 2% of clinic appointments. To further examine this, a bespoke online survey will be distributed to physiotherapists across the 19 UK Adult SMA REACH sites.

Data relating to assessment methods, treatment strategies, and perceived barriers to successful management will be captured. A combination of nominal and ordinal data will be generated, as well as free text responses to ensure detail and nuanced information is retained. Descriptive statistical analysis will be used to create a set of service-related conclusions, with simple, graphical depiction of the data. The findings will determine the current scope of practice in tertiary care centres nationally, potentially revealing inconsistencies in service provision and identifying specific training and resource needs.

This work directly addresses a gap in our knowledge around neuromuscular physiotherapy management of mechanical jaw restriction in SMA. It is hoped the generated evidence will prompt knowledge sharing not only within the UK, but internationally. Implementing a more consistent approach to the assessment and management of jaw mobility is a necessary step towards defining new standards of care for SMA, reflecting the complex, evolving needs of those living longer with the condition, in a new era of treatment.

P105

Medical emergencies in SMA: Outcomes of SMA Europe's 1st International Clinical Care Symposium

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Spinal muscular atrophy (SMA) is a progressive neuromuscular condition that predisposes individuals to acute, potentially life-threatening medical emergencies, including respiratory insufficiency (e.g., upper airway obstruction, hypoventilation), choking, fasting-related complications. Such emergencies may require lifesaving first aid skills and tools that are not routinely available to people living with SMA and caregivers. When urgent hospitalisation is needed, patients often encounter healthcare staff unfamiliar with SMA-specific complications, further increasing risk. Although some educational materials and national guidelines exist, consistent approaches remain lacking across different clinics and countries.

To address these gaps, SMA Europe launched its ***1st International Clinical Care Symposium on SMA,*** titled "***Medical Emergencies in SMA: pathophysiology, prevention, and response***", held in Milan on 29-30 August 2025. The event gathered multidisciplinary SMA experts (including physicians, nurses, physiotherapists, occupational therapists, nutritionists, speech specialists), researchers, patient advocates, and industry representatives. Main sessions focused on respiratory insufficiency, metabolic disturbances, and bulbar dysfunction. A dedicated session showcased clinicians from seven European and non-European countries who shared best practices and highlighted gaps in the prevention and management of acute events within their healthcare systems. Practical workshops engaged physiotherapists, patient advocates and HCPs, while a specialist workshop reviewed existing national guidelines and protocols on emergencies, summarised gaps or challenges in their application and initiated a working group to develop aligned international protocols for emergency response strategies.

The symposium, which was also livestreamed, reached around 200 participants from 35 countries across four continents, marked the first global initiative to focus specifically on SMA-related medical emergencies.

Building on its outcomes, SMA Europe and the working group are developing concrete outputs to strengthen the prevention and management of SMA-related medical emergencies, ultimately benefiting clinicians, researchers, patients, and caregivers worldwide.

P107

"From caregiver to playmate": A parent training model for treated children with Spinal Muscular Atrophy

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In our experience with parents of children affected by SMA, a recurrent difficulty has been observed: parents often struggle to dedicate time to relational play that is not exclusively oriented toward rehabilitation.
The aim of this abstract is to describe a training protocol designed to promote parental empowerment and enhance parent–child interactions in a preventive perspective, reducing the risk of neurodevelopmental disorders.
The program combines a family-centred care approach with a play-based methodology, delivered through counseling sessions focused on play. A multidisciplinary team provided practical support to caregivers, with the ambition of sustaining play activities within a developmental framework.
A secondary aim is to transfer the outcomes of this training to the experimentation of peer-group play activities.

This descriptive–observational study involved 16 parents of children with SMA type I (aged 9–36 months). Assessments were conducted at baseline (T0) and after 6 months (T1) using the Vineland Adaptive Behavior Scales-II, the SMA-Checklist and the SMA&PLAY Parent Questionnaire (internal measurement instruments). Additional resources, including a dedicated website and an illustrative brochure, were made available.

Research results are encouraging and stress the value of the multidisciplinary team as a promoter of the parent–child play relationship. In particular, the training appears to positively contribute to the child's communicative and relational development, thereby supporting the prevention of unfavorable developmental trajectories in this domain, which is considered at risk in children with SMA.

Within a family-centred framework, early parental habilitation and the promotion of caregiver well-being emerge as crucial factors for preventing alterations in developmental trajectories in the context of neuromuscular disorders.
In the last year, some experiments have been started at our center which have promoted group play activities between parents and children with the same characteristics.
Further investigations will be useful to consolidate robustness and implement the results obtained.

P109

Minimal invasive orthopaedic surgery in children with SMA - Early results in hip and knee joints

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Prior to Disease Modifying Therapies (DMTs), Orthopaedic Surgical Intervention in children with Spinal Muscular Atrophy (SMA) were rarely indicated due to high rates of recurrence, therapeutic failure and overall lack of symptoms. There is however increasing evidence that the emerging new cohort of patients following treatment with DMT, can experience pain or discomfort associated with hip disease. Although the exact natural history of orthopaedic problems is still unknown, prevention of both hip displacement as well as knee contractures and maintenance or improvement of the acquired mobility has prompted renewed interest in both conservative and surgical management strategies.

This is the first report in the literature of early results of minimal invasive orthopaedic surgery (MIOS) in hip and knee joints in children with SMA. Guided growth surgery to hip joints (medial proximal femoral hemi-epiphysiodesis) was performed in an attempt to stop hip migration, prevent dislocation and potentially correct/ reverse hip displacement. In addition, guided growth surgery to knee joints (distal anterior femoral hemi-epiphysiodesis) was undertaken to stop deterioration of fixed knee contractures and potentially correct the existing deformities in order to maintain and improve range of movement, independence, standing ability and overall mobility.

A total of 7 patients (4 SMA I, 2 SMA II and 1 SMA III) underwent MIOS in at least 2 joints - both hips(n:3), both knees(n:2) and both Hips and knees(n:2). Mean age at time of procedure was 5.6 years (3.8 – 10.4). Pre-operative x-ray showed a mean hip migration index of 35% (20 – 50%) on the right and 37% (20 – 50%) on the left. The pre-operative fixed knee flexion deformity had a mean value of 20 degrees (range: 15 - 25).
All patients came for their orthopaedic surgery on the day of the procedure and went home the following day. Their post-operative recovery was uneventful with no surgical complications recorded. All patients resumed their baseline activities, including sitting, standing, walking where applicable and routine care, within 24 hours after the procedure. Pain was effectively managed with standard analgesia, with no requirement for treatment escalation after surgery.
Regarding motor function and functional scales, all patients maintained the same WHO mobility classification. Among the 3/5 patients that underwent hip guided growth, with available follow-up data, results on both the Revised Hammersmith Scale (RHS) and the Hammersmith Functional Motor Scale Expanded (HFMSE) remained stable 4 months after the interventions.

Minimal Invasive Orthopaedic surgery in hip and knee joints in children with SMA is a safe surgical procedure allowing immediate return to full pre-operative function. It is a minimal invasive prophylactic surgical intervention with low post-operative complications, fast recovery and the potential to benefit children with SMA.

P113

SMA Care UK: Ensuring best hip management in individuals with SMA across the UK

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The 2018 international care recommendations for spinal muscular atrophy (SMA) were published prior to the availability of disease-modifying treatments (DMTs), which have significantly altered the clinical course, phenotype and prognosis of SMA. These guidelines, intended as a global minimum standard of care, were largely focused on paediatric populations and did not account for the novel and evolving phenotypes, now observed as a result of treatment advances.

SMA Care UK is a collaborative initiative involving healthcare professionals, people living with SMA and other stakeholders. Its goal is to update evidence-based standards of care and harmonise best practice in response to the priorities of the SMA community and the changing landscape of SMA.

While the 2018 international standards of care provided a foundation for musculoskeletal management in SMA, hip management was not a primary focus. Individuals with SMA, particularly non-ambulatory patients, are at high risk of hip instability, subluxation and dislocation, driven by muscle weakness, immobility, contractures and scoliosis. Hip displacement can cause pain, seating difficulties and reduced quality of life. In the era of DMTs, which extend survival and broaden phenotypes, hip management remains essential and requires individualised conservative and surgical approaches. These factors underscore the need for clinical guidance to support systematic assessment, monitoring and management of hip health across the paediatric-to-adult spectrum.
In response, individuals living with SMA, expert adult and paediatric healthcare professionals, including Neurologists, Orthopaedic Surgeons, Neuromuscular Physiotherapists and an Orthotist, have undertaken a comprehensive review of the current evidence and practice for hip management in SMA. Drawing on emerging data, evolving clinical experience and identified areas of unmet need, the group will develop guidance covering assessment, monitoring and therapeutic interventions. The group is working with relevant professional bodies and NICE, so that guidance can be endorsed and published once consensus is achieved.

In parallel, gaps in evidence are being highlighted and strategies will be developed to address these, including future evidence-gathering and collaboration with international networks to ensure that updated guidance remains aligned with global best practice.

P115

CSF biomarkers show blood-spinal cord barrier dysfunction in treated Type 3 SMA patients

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Spinal muscular atrophy (SMA) is a motor neuron disease, however the survival motor neuron (SMN) protein deficiency which causes the condition, is cell ubiquitous. As a result, SMA exerts widespread effects across multiple tissues and organ systems. Vascular pathology, in particular, has the capacity to exacerbate disease progression, making it a critical area for investigation.
Our previous work revealed microvascular defects in human post-mortem, Type 1 SMA spinal cord, including increased vascular density, ultrastructural endothelial damage, and disruption of the blood–spinal cord barrier (BSCB). Histological evidence of BSCB leakage suggests that entry of toxic blood components into the neural environment could accelerate motor neuron degeneration in SMA. However, whether these vascular disruptions persist following treatment in patients remains unknown.

To investigate potential biomarkers of BSCB compromise in patients, a preliminary analysis was carried out on CSF collected from three Type 3 SMA patients (aged 10–17 years) receiving Nusinersen treatment. Control CSF was obtained from consenting adults undergoing diagnostic lumbar puncture, with no biochemical abnormalities or neuroinflammation. Differential protein abundance between SMA and control CSF was assessed using diaPASEF label-free quantitative mass spectrometry (MS). Bioinformatic analysis with Ingenuity Pathway Analysis (IPA) was used to identify altered cellular and molecular pathways.

MS identified 1,361 proteins, of which 177 showed significant changes in abundance. Eighty-five proteins were found to be significantly increased in SMA CSF, with the largest fold changes observed in collagen 1(III), collagen 1(I), and periostin - markers of extracellular matrix (ECM) remodelling. IPA predicted activation of ECM accumulation and TGF-–driven remodelling pathways, and inhibition of pathways related to neuronal density, endothelial proliferation and development, intercellular junction formation, and cerebrovascular function, consistent with both neuronal loss and impaired vascular homeostasis. In addition, elevated levels of blood-associated coagulation factors (F9, PROS1, ITIH1/2), apolipoproteins (APOE, APOL1), lipoprotein transfer proteins (PLTP, CLU), and vitronectin (VTN) in SMA patient CSF suggest BSCB dysfunction, and leakage of plasma components into the CSF.

The entry of toxic blood proteins into the CNS may drive or exacerbate neuronal pathology, implicating BSCB breakdown as a potential contributor to motor neuron loss in SMA. While current therapies were developed to rescue motor neurons, they may not target vascular or BSCB-associated cells, allowing novel pathological features to emerge as treated patients age. Future therapeutic strategies should therefore include approaches to restore barrier integrity, providing more comprehensive disease management and improving long-term outcomes for patients.

P117

Unexpected sources of biomarkers and therapeutic targets from epitranscriptional ribosome heterogeneity

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The recent approval of three SMN-dependent therapies marks a major breakthrough for the SMA community, extending life expectancy and improving motor functions of individuals living with SMA. However, the introduction of these therapies calls for a step back to basic research. Understanding the complete spectrum of SMN functions is essential in the post-therapy SMA era, to provide clinicians with the means to offer appropriate counselling on disease progression and therapy responses to individuals living with SMA and their caregivers. To date, such means to monitor disease progression and response to therapies have not been identified yet and no SMA-specific and mechanism-based molecular biomarker is available for clinical testing.

Beyond its canonical role, SMN protein associates with ribosomes, the macromolecular machineries that produce proteins. Ribosomes play an active role in the regulation of gene expression through intricate interactions with external proteins such as SMN and modulation of their components, including ribosomal proteins, rRNA and their modifications. Although still largely unexplored, ribosome heterogeneity holds great promise as a source of therapeutic targets and biomarkers in human disease. The SMN-ribosome platform modulates the translation of a specific set of mRNAs and, consequently, the cellular proteome.

Among the protein interactors of the SMN-ribosome platform, we identified the methyltransferase fibrillarin which is responsible for the deposition of 2'-O-methylations (2'-O-me) on rRNA. Prompted by these findings, we exploited RiboMethSeq to explore the hypothesis that loss of the SMN-ribosome platform could alter rRNA 2'-O-me landscape. Our results suggest that both ***in vivo*** and ***in vitro*** in murine and patient-derived cultures, low levels of SMN are associated with alterations in the 2'Ome landscape, with major differences affecting known developmentally regulated 2'-O-me. Strikingly, the rRNA 2'O methylome obtained from patient's derived fibroblasts can be used to stratify the patients according to their disease severity.

Taken together, our findings uncover putative SMA-specific molecular biomarkers within the novel SMN-ribosome framework. We envision that rRNA 2-O-methylation signatures may represent a pioneering class of molecular biomarkers with potential implications in other diseases.

P119

A novel ECL assay for monitoring SMN protein levels in SMA patient samples

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Despite the availability of three SMN-targeting therapies for spinal muscular atrophy (SMA), clinical outcomes vary considerably between patients. This highlights the need for reliable biomarkers to predict treatment efficacy and monitor disease progression. Several classes of biomarkers have previously been investigated, such as markers of neurodegeneration, inflammation, metabolism, and circulating microRNAs. However, the direct quantification of SMN protein has been less extensively explored, due to difficulties detecting it in patient serum and CSF. To address this, we developed a novel electrochemiluminescence (ECL) assay for sensitive and specific quantification of SMN protein in patient samples. Using this assay, we quantified and compared SMN levels in patient-derived fibroblasts, whole blood, serum, and in relevant mouse tissues including brain and muscle. In patient fibroblasts, ECL measurements showed strong concordance with established techniques such as western blot and ELISA. In patient whole blood and serum samples, SMN could not be measured with either ELISA or western blot. In contrast, with ECL we were able to measure SMN robustly and reproducibly in both serum and whole blood. This shows that both sample types can be used to monitor systemic SMN levels. Additionally, our analyses demonstrated sufficient sensitivity to capture biologically relevant differences across sample types and patient-derived materials. Our findings suggest that this ECL-based assay can serve as a practical tool to monitor SMN protein levels in patients before and after treatment, which we will further explore in followup analyses. This approach provides an additional way forward to evaluate and include SMN as a biomarker for disease and treatment outcomes.

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Feasibility and reproducibility of continuous passive mode isokinetic dynamometry in children with SMA

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Accurate assessment of muscle strength is crucial for evaluating disease progression and treatment efficacy in neuromuscular diseases (NMD). While isokinetic dynamometry provides these capabilities, its use is challenging in patients with moderate and severe muscle weakness (MRC 2-4). We propose the continuous passive mode (CPM) as an alternative method applicable to a broader patient population.

The aim of this study is to determine the feasibility and reproducibility of isokinetic dynamometry in CPM in children with SMA.

This study used a test-retest design, with each session comprising two sets of five repetitions of CPM elbow flexion-extension at 90 °/s. During the first 'passive' set, participants were instructed to fully relax, while the dynamometer passively moved their arm through the predefined range of motion. In the second, 'active-assisted' set, participants were instructed to actively flex and extent their arm in the direction of the passive movement of the handle.
Net peak torque was derived by subtracting the passive torque from the active-assisted torque curve. Data were $\log_{10}$ transformed to correct for skewness and Bland-Altman plots were used to check for heteroscedasticy. Reliability was evaluated by using the Intraclass Correlation Coefficient (ICC), while the Standard Error of Measurement (SEM%) and Smallest Detectable Change (SDC%) quantified reproducibility. Feasibility was assessed by acceptability and completion rates.

We enrolled 21 children with SMA (age: 11.2 ± 2.6 years). Acceptability was high (mean Visual Analog Scae score (0-100): 81(17) mm and completion rates were 95% for elbow flexion (N=20) and 81% for elbow extension (N=17). Reliability was excellent for both elbow flexion (ICC 0.987, 95% CI 0.968-0.995) and elbow extension (ICC 0.964, 95% CI 0.866-0.988). A significant test-retest difference was observed for elbow extension (mean difference -0.079 (95% CI -0.14 to -0.014, p = 0.02). Measurement error and smallest detectable difference were 9% and 26% for elbow flexion, and 24% and 66% for extension, respectively.

Our findings demonstrate high feasibility and excellent test-retest reliability of CPM elbow flexion and extension in children with SMA. Reliability was comparable to other isokinetic dynamometry methods in children with NMD, though measurement error was greater for elbow extension than for elbow flexion.

CPM is a feasible and reliable tool to measure torque in a large range of patients with SMA with strength ranging from MRC 2 to 5.

P123

A high-throughput microfluidic MEA platform to model SMA-specific neuromuscular junctions and identify electrophysiological biomarkers

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Spinal Muscular Atrophy (SMA) presents various clinical forms ranging from severe (type 0/I) to milder (type III/IV) phenotypes. Since SMA lacks curative treatment, understanding the mechanisms underlying this heterogeneity and identifying new therapeutic candidates is crucial. To this end, we developed a novel 32-well microfluidic platform with microelectrodes (MEA) to reconstruct human neuromuscular junctions (hNMJs) in vitro and monitor their electrophysiological activity. Our aim is to establish subtype-specific NMJ models and assess their treatment response based on electrophysiological profiling.

NMJs were successfully reconstructed using hiPSC-derived motor neurons and myotubes from patients with different SMA subtypes and healthy controls. Motor neurons (MNs) and myotubes were seeded in separate microfluidic chambers connected by 4µm-wide, 500µm-long microchannels, replicating in vivo motor neuron-muscle distance. To ensure muscle attachment and cell polarization, 1µm-deep grooves were etched in the muscle chamber's insulation layer. A subset of 2 electrodes is positioned in each chamber to assess muscle and motor neuron activity separately, with a total of 128 electrodes across the device.

Initial co-culture experiments generated mature neuromuscular junctions (NMJs), based on previously published data from our laboratory. Mature NMJs were identified by -bungarotoxin (AChR clusters) and SMI-32 (axonal marker) staining. Muscle fibers were stained with an alpha-actinin antibody to assess muscle maturation. Following NMJ reconstruction, action potentials from both MNs and muscles were detected during electrophysiological experiments, further confirming cell maturation.

Our objective is now to characterize electrophysiological signatures across different SMA types. To achieve this, we are developing a custom pipeline for artifact removal, spike detection and feature extraction, focusing on parameters such as firing rate, inter-spike interval or burst rate. Preliminary results using 20-minute recordings of 16 Healthy and 16 type II SMA conditions showed that SMA samples exhibit higher variability in ISI values, decreased firing rate and higher intra-burst rate which may reflect MN loss and compensatory hyperexcitability. From these features, we are building a comprehensive database, then used to train machine learning classification algorithms to distinguish healthy versus pathological recordings. Preliminary results showed that the Random Forest algorithm was the most effective for this task, scoring best in both accuracy and cross-validation.

Our goal for this platform is to offer a robust tool to automatically detect defects in electrical activity and subsequently enable pharmacological screening to evaluate the potential candidate compounds to restore healthy electrophysiological profiles. The platform also enables cross-culture experiments to investigate cell-type specific contributions to SMA pathology.

P125

Investigation of intracellular localization and secretion of SMN by modulating alpha tubulin detyrosination

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Spinal muscular atrophy (SMA) is a rare neurodegenerative disease, caused by deficiency of survival motor neuron (SMN) protein. SMN is ubiquitously expressed, localized in the nucleus and cytoplasm, and secreted to extracellular environment. SMN deficiency leads to cytoskeleton perturbations, including microtubules. Microtubules function in motility-required cellular processes, including organelle positioning and intracellular vesicle trafficking. Microtubules are polar and dynamic filaments composed of alpha () and beta (β) tubulin proteins, both of which possess several post-translational modifications (PTM). Detyrosination, which refers to the removal of terminal tyrosine residue from tubulin, is one of the PTM indicating stabile microtubules. After microtubule depolymerization, detyrosinated tubulins are re-tyrosinated by an enzyme called tubulin tyrosine ligase (TTL). In an in vitro SMA model, we previously demonstrated decreased level of detyrosinated tubulin and upregulation of TTL. Detyrosination affects interaction of motor proteins with microtubules and influences intracellular transport. Considering widespread localizations of SMN, we hypothesized that modulating tubulin detyrosination could have an impact on SMN distribution. To increase tubulin detyrosination, we used siRNA mediated gene silencing approach and knock down TTL in SMN-depleted motor neuron like NSC34 cells. Western blot studies demonstrated a significant upregulation in tubulin detyrosination in co-knock down cells compared to cells with SMN knock down only. In co-knock down cells, endogenous SMN distribution was analyzed by immunostaining, and quantitative image analysis showed that nuclear SMN was not altered. However, the level of cytoplasmic SMN decreased in the cell body, while it increased at the neurite tip. We also collected media of these cells and examined extracellular SMN level contained in TCA precipitates. Western blot studies showed that extracellular SMN level were significantly increased in the media of co-knock down cells compared to the cells with SMN knock down only. Our findings indicate that microtubule dysregulation influences SMN localization and secretion, and suggest that modulating -tubulin PTMs may offer a potential strategy to restore microtubule-dependent cellular pathologies in SMA. Studies are ongoing to understand the mechanistic link between microtubule detyrosination and SMN distribution.

P127

SMN–Anxa2 mRNA interaction regulates axonal localization in a developmental stage-dependent manner

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Spinal Muscular Atrophy (SMA) is an autosomal recessive motor neuron disease characterized by the selective degeneration of lower -motor neurons (MNs), disruption of neuromuscular junctions (NMJs), and progressive muscle weakness leading to paralysis and premature death. SMA is caused by deletions or mutations in the SMN1 gene, resulting in reduced levels of Survival Motor Neuron (SMN) protein. Although SMN is ubiquitously expressed and best known for its essential role in the assembly of spliceosomal small nuclear ribonucleoproteins (snRNPs), splicing defects alone fail to explain the selective vulnerability of MNs. Mounting evidence suggests that SMN has additional neuronal functions, particularly in axonal mRNA trafficking and local translation, which are essential for sustaining growth cone dynamics, synapse formation, and axonal maintenance. Among the transcripts regulated by SMN, Anxa2 mRNA has emerged as a particularly compelling candidate. It contains a conserved axonal targeting sequence in close proximity to a direct SMN-binding motif, a unique feature among SMN-regulated transcripts. Anxa2 encodes Annexin A2 (ANXA2), a Ca^{2+}-dependent phospholipid-binding protein with scaffolding functions at the cytoskeleton–membrane interface. In neurons, ANXA2 is enriched at growth cones and axonal branch points, where it participates in actin remodeling and microtubule stabilization—two processes critically impaired in SMA. This raised the hypothesis that impaired axonal localization of Anxa2 mRNA may contribute to cytoskeletal defects underlying motor neuron degeneration. To test this hypothesis, we employed human induced pluripotent stem cell (iPSC)-derived MNs from SMA patients and healthy controls. We implemented single-molecule fluorescence in situ hybridization (smFISH) combined with semi-automated spot detection to quantify Anxa2 mRNA density specifically within axons across developmental stages. This approach revealed a marked reduction in axonal Anxa2 mRNA in SMA MNs compared to controls, with the most pronounced defects occurring during early neuronal development. Importantly, colocalization analyses with SMN immunostaining, as well as RNA-proximity ligation assays (RNA-PLA), demonstrated that SMN interacts directly with Anxa2 mRNA in a temporally restricted manner. The interaction peaked during early developmental stages, coinciding with periods of intense axon growth and branch formation. To further probe the functional relevance of this interaction, we performed SMN overexpression experiments in SMA MNs. Restoration of SMN levels was sufficient to rescue axonal Anxa2 mRNA localization, but only when performed during early developmental stages. Late-stage overexpression failed to re-establish proper localization, suggesting that SMN-dependent Anxa2 transport is developmentally regulated and restricted to a critical temporal window.

P129

Differential cell-type-specific interactomics of the Survival of Motor Neuron (SMN) protein

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Proteins engage in several stable and transient interactions with other proteins defining their functional roles. This population of interactors form the interactome of a protein of interest, which can be experimentally determined by a combination of biochemical enrichment and mass-spectrometry-based techniques. We have previously characterized the interactome of the Survival of Motor Neuron (SMN) protein in murine neuronal cells. The interactome analysis was combined with other omics levels, i.e., proteome, translatome and metabolic data to unravel previously unknown causal disease mechanisms. By this approach, we were able to characterize dysregulated purine metabolism in children with SMA (Tapken et al., 2025, Brain). Here, we hypothesize that SMN is involved in both cell-type specific and common interactions. This was experimentally addressed in human embryonic kidney cells, skeletal muscle and control and SMA primary fibroblasts. As a result, we found interacting partners constitutively shaping the partnering landscape. Moreover, we identified cell-type specific interactions. In conclusion, SMN is engaged in several interactions reflecting its function in diverse molecular networks. This information is important to elucidate and characterize causal pathomechanisms in a system-wide context.

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Astrocytic inward rectifier potassium channel Kir4.1 dysfunction as a target for new therapeutic strategies in late-onset Spinal Muscular Atrophy

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In the pathogenesis of late-onset spinal muscular atrophy (SMA), increasing evidence suggests the involvement of non-neuronal cells, such as astrocytes. This study aimed to investigate the interaction between spinal astrocytes and motoneurons (MNs), focusing on the inwardly rectifying potassium channel Kir4.1 and the neurotrophin brain-derived neurotrophic factor (BDNF).

Using a mouse model of SMA and cell cultures of murine and human-induced astrocytes, we examined the expression and function of Kir4.1 and its impact on BDNF expression and release. Specific blockers were employed to probe a potential signaling pathway.
Our results demonstrated a reduction in the expression and function of Kir4.1 in spinal astrocytes (both murine and human). This reduction led to membrane depolarization, which triggered glutamate release and subsequent autocrine activation of metabotropic glutamate receptor 5 (mGluR5). This cascade activated calcium-dependent signaling, specifically the RAS/MEK pathway, which increased BDNF expression and release from the astrocytes. Additionally, BDNF was found to upregulate the expression of calcium-permeable GluA1 AMPA receptors in spinal MNs, thereby increasing their susceptibility to glutamate-induced toxicity, a phenomenon we have previously linked to EAAT-1-mediated glutamate uptake (Schmitt et al., 2023). Through drug repurposing assays, we identified several approved drugs, including Valproate, Salirasib, and Perampanel, as potential modulators of this signaling pathway, targeting astrocytes and MNs. In vivo administration of these drugs effectively prevented motoneuron loss in late-onset SMA mice, although they did not lead to an increase in the functional levels of survival motor neuron (SMN) protein.

These findings underscore the pivotal role of spinal astrocytes in the pathogenesis of late-onset SMA and suggest considerable therapeutic potential in targeting these cells.

P133

Motoneuron deafferentation in SMA is driven by necroptotic- and autophagic-like mechanisms and prevented by 4-aminopyridine treatment

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Spinal muscular atrophy (SMA) is an autosomal recessive disorder affecting -motoneurons (MNs) in the spinal cord and brainstem, leading to MN cell death and muscle weakness and atrophy. SMA results from a deficiency of survival motor neuron (SMN) protein due to mutations or deletion of SMN1 gene. We have previously shown that MN degeneration in SMA is accompanied by the loss of central synapses, leading to early MN deafferentation. These disrupted synapses exhibited morphological features that fit well with an autophagic/phagocytic process. Here, we further investigated the cellular mechanisms underlying the synaptic elimination responsible for MN deafferentation in SMA pathology.

The SMNΔ7 mouse, a model of severe SMA was used. Wild-type (WT) and mutant (SMNΔ7) mice at postnatal days 5 and 14 (presymptomatic and end stages of SMA disease, respectively) were analyzed. Immunocytochemical, ultrastructural, and western blot analyses were performed in spinal cord samples. Antibodies were used against different proteins involved in autophagy and necroptosis, such as beclin-1 and LC3 (autophagy markers), p-MLKL (necroptosis marker), Flotillin-1, CD63 and CD81 (exosomal markers), LAMP-1 (lysosomal marker) and C1Q (protein of the complement system). Moreover, antibodies against Iba1 and CD68 (for microglia), GFAP and S100b (for astroglia), and phosphatidyl serine (PS, apoptosis marker) were used. In addition, the impact of implementing MN activity by chronic 4-aminopyridine (4-AP) treatment on these mechanisms was also assessed.

Compared to spinal cord samples of WT animals, those of SMA mice displayed significantly increased expression in p-MLKL, Beclin-1, and Flotillin-1 in synapses and dendrites. In addition, glial cells exhibited increased activation in SMA, which appeared to be related to synapse pruning. Ultrastructural analysis revealed that synapse elimination involved neuronal (dendritic) phagocytosis of degenerating synapses. Disrupted presynaptic structures were found engulfed by swollen dendrites containing autophagic-like vacuoles. Astroglial profiles were often seen enwrapping dendrites that contain synaptic debris, whereas microglia were only moderately activated for synaptic removal. These alterations were prevented with 4-AP treatment.

Our findings indicate that necroptosis/autophagy and glial cell activation are key mechanisms in MN deafferentation in SMA, and that this pathological process can be counteracted by increasing activity after 4-AP treatment.

P135

Evaluation of the neurotrophic potential of B-Raf Gain-of-Function mutants in an *in vitro* system of neurodegeneration

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Neurotrophic factors are critical for neuronal homeostasis by promoting survival, differentiation, and neurogenesis through intracellular signaling. The serine/threonine kinase B-Raf is a key mediator, activating the MEK/ERK pathway. In Spinal Muscular Atrophy (SMA), B-Raf levels are reduced, contributing to pathology, whereas elevating B-Raf enhances neuronal survival, and locomotion in ***C. elegans***. Notably, a ***C. elegans*** orthologue of a B-Raf gain-of-function (GoF) mutant further amplified these effects, suggesting therapeutic potential in neurodegenerative diseases. To systematically assess B-Raf GoF activity, we generated a library of mutants and tested them in NSC34 motor neuron-like cells under four degenerative conditions: kainic acid, staurosporine, serum reduction, and an NSC34 cells with reduced SMN levels (NSC34 SMN_{kd}). Primary embryonic motor neurons were also established and exposed to the same conditions. Kainic acid was insufficient to induce degeneration in NSC34 cells, while staurosporine and NSC34 SMN_{kd} cells produced clear phenotypes. Several B-Raf GoF mutants were successfully created using site-directed mutagenesis. In parallel, embryonic motor neurons were isolated and characterized from murine spinal cords, providing a primary culture system for further validation. Using Cell Profiler™, we developed an automated platform to evaluate neurodegenerative phenotypes and systematically test B-Raf GoF mutants for their neuroprotective properties.

P137

Astrocytic Alterations in 5q Spinal Muscular Atrophy: A Human Cell Model Approach

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Astrocytic dysfunction has been identified as an early event preceding motor neuron degeneration in 5q-SMA and may contribute to the variability of disease progression and treatment response. Current SMN-targeted therapies show limited efficacy in advanced disease stages, underlining the need to explore SMN-independent mechanisms. This project focuses on deciphering patient-specific astrocytic disease mechanisms using a human cell culture model.

Adults with genetically confirmed 5q-SMA are clinically and genetically characterized, including motor function scores, prior therapies, disease duration, and ***SMN2*** copy number. Peripheral blood mononuclear cells (PBMCs) are isolated, virally transfected, and differentiated via neural precursor cells into astrocytes. Astrocytes from healthy controls are generated in parallel. Patient- and control-derived astrocytes are analyzed with respect to morphology, expression of astrocytic marker proteins, and functional properties. Proteomic profiles are correlated with clinical data to identify astrocytic disease signatures.

Generation of patient- and control-derived astrocytes from PBMCs was successful. Induced astrocytes expressed typical astrocytic markers and displayed typical electrophysiological properties. Comparative analyses between SMA and control astrocytes as well as first proteomic findings will be presented.

We established patient-specific astrocytes from blood-derived cells of adults with SMA, enabling the investigation of astrocytic disease mechanisms in a human model through a simple and minimally invasive approach. These astrocytic mechanisms, so far unexplored and not targeted by current therapies, may contribute to the variability in clinical progression and treatment response to gene-based therapies.

P139

Standardized outcome measures for SMA – the educational concept within the SMArtCARE registry

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SMArtCARE is a disease-specific registry, collecting longitudinal data on all available SMA patients independent of their actual treatment. Data are collected during routine patient visits as real-world-outcome data and items for data collection are aligned with the international consensus for SMA registries. For the long-term follow-up of SMA patients, standardized evaluation of motor function is key. For this purpose, several standardized outcome measures have been developed and validated for SMA patients. According to age and severity of the disease, we established recommendations for these physiotherapeutic assessments selecting between the CHOP INTEND, HFMSE, RULM and the 6-minute-walk-test. For all assessments, a detailed protocol and scoring system is provided.
Since 2019, SMArtCARE has offered 17 workshops and 16 webinars for the SMArtCARE community with a total of 1158 participants. In these workshops, physiotherapists practice the implementation and evaluation criteria of the individual motor function tests. The level of instruction is geared toward beginners and advanced users. The workshops were complemented by presentations on various topics related to SMA. Further, a certification system for physiotherapists was developed via an online learning platform. The certification system is based on a multiple-choice questionnaire. All physiotherapists who have participated in SMArtCARE training workshops or webinars get access to this certification system to proof their skills.

The training concept and certification system for physiotherapists contributes to further improve data quality within the SMArtCARE registry.

P141

Struggled between mental & physical strength: A struggle of SMA patients

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Spinal Muscular Atrophy (SMA) is rare genetic disease that gradually makes the muscle weaker day by day. It also reduces breathing and swallowing abilities. Fortunately, SMA does not affect brain and intellectual abilities. This unique characteristic of SMA creates a profound paradox for SMA patients. Their creativity and emotions remain intact but physical condition does not allow them to express their creative mind.

For many SMA patients especially children this imbalance between mental and physical ability results in deep frustration and challenges. They can dream like their siblings and friends but sometimes cannot perform very basic tasks by themselves like holding pen/pencil, taking books out of the bag in class. They are very fond of playing physical games like football and cricket but they are not capable of lifting the ball in their hands.

This gap between mind and body can be seen in both their daily and education life. Like their daily life, their educational life may also need assistance from others. But in most cases, it becomes difficult in developing countries to find someone who can help a patient in class. This often forces them to keep themselves away from peers, where their talents remain hidden, unrecognized, and underutilized.

The difficulties extend into emotional well-being as well. Their intellectual ability may sometimes misunderstand due to their physical condition. This undermines their confidence and sometimes they confined themselves inside the house. Families witnessing the brilliance of their loved ones but struggling to find pathways for them to thrive.

These are the real experience of SMA patients they face daily in their own house, school, outdoors. We need to help them prove their worth by using their intelligence rather than their physical strength.

By breaking down barriers, we can empower SMA patients to share their intelligence, creativity, and human spirit—reminding us that while the body may be limited, the mind remains limitless.

P143
Real-world motor function outcomes with risdiplam in Types 2 and 3 SMA: A systematic literature review and meta-analysis

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Risdiplam (EVRYSDI®) is approved for the treatment of spinal muscular atrophy (SMA). Efficacy data are available in adults from the SUNFISH (NCT02908685; 2–25 years) and JEWELFISH (NCT03032172; 1–60 years) clinical trials; however, real-world (RW) evidence of risdiplam is limited, but the body of literature is growing.

A systematic literature review (SLR) was conducted to review RW outcomes in adults with SMA treated with risdiplam. Electronic databases (Embase, MEDLINE, Evidence-Based Medicine Reviews) were searched from database inception to 30th October 2024. A total of 42 RW studies of risdiplam were identified that reported a wide range of recognised motor function measures.

A feasibility analysis was conducted to determine if a meta-analysis could be performed using the data obtained in the SLR. Pooled analysis of Revised Upper Limb Module (RULM) and Hammersmith Functional Motor Scale – Expanded (HFMSE) outcomes was feasible but further analysis of 32-item Motor Function Measure and the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders outcomes was not recommended due to the small number of studies reporting results of these assessments (n=2, each). Twelve studies reported motor function using the RULM and/or HFMSE in individuals with Types 2 and 3 SMA.

A targeted literature search was then performed in July 2025 to identify additional studies reporting RULM and HFMSE outcomes in individuals with Types 2 and 3 SMA published after October 2024. An additional three studies were identified.

Out of 15 studies identified, 11 (74%) were single centre, two (13%) were multicentre and two (13%) did not report the study setting; all were observational in nature (eight [53%] prospective, six [40%] retrospective and one [7%] hybrid [prospective and retrospective]). The studies included a total of 344 patients with Types 2 and 3 SMA. Of the 15 studies, 13 were conducted in Europe (Belgium n=1, Croatia n=3, France n=1, Germany n=3, Greece n=1, Ireland n=1, Italy n=2, Portugal n=1), and two were conducted outside Europe (Iran n=1, Israel n=1). Of 15 studies, nine reported data for both the HFMSE and RULM, three reported data only for the HFMSE and three reported data only for the RULM. Consequently, RULM and HFMSE were each reported in 12 studies. RULM and HFMSE outcomes in these studies will be reported in two meta-analyses. Findings will provide further insights into the RW effectiveness of risdiplam in adult individuals with SMA.

P145

Adult SMA REACH: A real-world data collection study and ready-made infrastructure to support research and improvement initiatives in SMA

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Adult SMA REACH a Research and Clinical Hub that established a collaborative clinical network in 2020 across 18 clinical sites in the UK, patient advocacy groups, regulators, and industry. It also established a longitudinal observational real-world data (RWD) collection study, collecting clinical data and outcome measures from adult SMA patients in the UK. SMA treatments Nusinersen and Risdiplam are available through Managed Access Agreements (MAA); Adult SMA REACH is responsible for capturing and reporting data to UK regulatory authorities to support their review of drug efficacy. The final data cuts for both MAA's have now passed and Adult SMA REACH is in a position to grow; as a ready-made infrastructure to inform research questions in the UK, it is already currently supporting a number of initiatives. The aims of Adult SMA REACH are to better understand the natural history of adult SMA, evolving phenotypes and the impact of new therapies. Data is collected from clinical sites via a centralised online database. Using innovative data modelling techniques, we created an automated software for data validation, consistency checks, completeness analysis and treatment tracking. This allows us to continuously monitor evolving datasets, maximising the quality of collected data. Anonymised data can be provided to support research following submission of a data request which must receive approval from the steering committee. Data collected via Adult SMA REACH has supported research related to access to care; analysis of age at diagnosis, prevalence, and mortality; baseline characterisation of adults; and safety/efficacy analyses of available treatments. In addition to this, it is supporting the SMA Care UK initiative which aims to update and implement the Standards of Care for SMA patients. A pregnancy sub-study has also recently been established to characterise the effects of Nusinersen on pregnant women and the infants born to them. Adult SMA REACH is a valuable infrastructure to support SMA research, ultimately optimising patient care, advancing therapy approvals and broadening the understanding of the disease.

P147

Assessing unmet needs and disease burden among treated and untreated adults with SMA

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The advent of disease-modifying therapies (DMTs) for spinal muscular atrophy (SMA) has led to improved survival and motor function, particularly among those who received treatment early in life and before disease progression. Despite widespread availability, not all individuals with SMA receive treatment, and little is known about how treated and untreated populations differ in demographics, disease characteristics, and functional outcomes. Understanding these differences may inform clinical practice, future research initiatives, and strategies to address barriers to care.

Data was collected from the Cure SMA Unmet Needs Among Adults Across the Healthcare Spectrum survey between June 24th - July 28th, 2025. The survey was open to U.S. adults with 5q-SMA, and all data was self-reported. The analysis compared demographics and disease severity, current symptoms, and activities of daily living (ADLs) reported as difficult to complete between treated and untreated individuals.

268 individuals completed the survey and provided treatment information. The majority (89%) reported ever receiving at least one DMT. Demographics were similar between the treated and untreated individuals with both groups being predominately white (84% vs. 83%), non-Hispanic (88% vs. 77%), and female (68% vs. 73%). On average, treated individuals were younger than untreated individuals at time of survey (38.4 years vs. 45.1 years). SMA type distribution varied between groups with 1% Type 1, 50% Type 2, 45% Type 3, and 3% Type 4 within the treated group, and 3% Type 1, 37% Type 2, 43% Type 3, 7% Type 4, and 10% unknown type within the untreated group. Although the overall distribution of ambulation categories was generally similar between groups, a higher proportion of treated individuals were unable to walk ≥ 10 steps with or without assistance compared to untreated (82% vs. 67%).

Muscle weakness in the arms (93% vs. 83%) and legs (98% vs. 93%), and difficulty with mobility (91% vs. 83%) were the most prevalent symptoms among both treated and untreated individuals. Reported ADLs that were most difficult to complete were similar among both groups, with the most prevalent difficult ADLs being "unexpected events that require more strength and/or energy to complete" (91% vs. 76%) and "managing the home" (84% vs. 79%).

This analysis serves as a baseline evaluation on the differences and similarities between untreated and treated individuals with SMA. Although treated and untreated individuals in this sample differed in age, SMA type distribution, and endurance with ambulation, both groups reported substantial functional limitations and disease burden. However, the untreated sample was relatively small, and results may not fully represent the broader SMA population. These findings highlight the need for continued research into therapies that further modify disease progression, as well as comprehensive care approaches to address the needs of individuals who do not receive treatment.

P149
Cardiac involvement in adults with Spinal Muscular Atrophy: A multi-centre audit of cardiac monitoring outcomes and complications

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Spinal muscular atrophy (SMA) is a genetic neuromuscular disorder caused by mutations in the SMN1 gene leading to reduced SMN protein levels. Whilst SMA predominantly affects motor neurons, there is an association of cardiac manifestations. SMN2 modifiers like Risdiplam, which has systemic bioavailability, may impact the cardiovascular system and requires monitoring for QT prolongation.

Audit of all SMA patients on disease modifying drugs across three regional centres (St George's, Salford and Sheffield) to assess the outcomes of cardiac monitoring.

A 24-month retrospective manual review of clinical notes and investigations across centres. Patients were categorised by SMA type and severity; concurrent disease modifying treatment; cardiac symptoms and cardiac investigations. All ECGs were reviewed by a cardiac electrophysiologist.

A total of 122 patients were identified. 105 (86.1%) had ECGs to review and of these 33 (31.4%) demonstrated an abnormality. 31% SMA type 2 (mean age 35) and 25% SMA type 3 (mean age 42). ECG abnormalities were 14 LVH criteria; 2 RVH criteria; 9 right bundle branch block; 1 right bundle branch block + left axis deviation; 1 first degree AV block; 1 atrial fibrillation; 8 with T wave inversions; 3 with ST depression and 7 prolonged QTc. Of these cases only one case was >480ms prolonged QT, who were reviewed by cardiology and have been diagnosed with congenital long QT. 17 (16.1%) patients required specialist cardiology assessment for their ECG/symptomatology. Echocardiograms demonstrated only 2 structural abnormalities: a 19-year-old (SMA type 1) with mild-mod mitral and tricuspid regurgitation and normal biventricular size and function; a 40-year-old (SMA type 2) with impaired right ventricular function and no left to right shunt identified. No arrhythmias were identified on holter monitoring in the 2-year period of notes review.

SMA patients require monitoring for cardiac manifestations. We have demonstrated over a quarter of SMA patients across 3 regional centres exhibit ECG abnormalities and over a 2-year period more than one in seven required cardiology input. With the advent of disease modifying therapy differentiating age-related vs primary SMA-associated cardiac manifestations becomes challenging. No patients on Risdiplam displayed concerning QT prolongation. Cardiac structural abnormalities were rare. One case of AF was identified, with no other concerning arrhythmias.

P151

Epidemiological characteristics of children with SMA in Croatia: Before and after newborn screening

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Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disorder caused by mutations in the ***SMN1*** gene, leading to the loss of -motor neurons in the anterior horns of the spinal cord and consequently progressive symmetrical muscle weakness. SMA was one of the most common inherited causes of early death due to respiratory failure. In Croatia, all three disease-modifying therapies (DMT) are available for children with SMA, facilitating increased production of the functional survival motor neuron (SMN) protein through different molecular mechanisms and administration methods. Early treatment initiation, which was made possible by newborn screening (NBS) for SMA, alters the natural disease course by halting progression, resulting in novel phenotypes and changing disease epidemiology.

This study aimed to determine the epidemiological characteristics of children with SMA in Croatia before and after the implementation of NBS in March 2023. We retrospectively analysed data from the Reference Center for Neuromuscular Diseases, examining NBS results, medical histories, and genetic analyses from the Dept. for Molecular Diagnostics of the Clinical Hospital Center Zagreb between 2000 and 2025. Currently, 54 patients aged 0-18 are under treatment at the Reference Center, with 47% of patients classified as type 1, 22% type 2, 13% type 3 and 18% detected through NBS. Our results characterize the epidemiological profile and functional assessment of children with SMA in Croatia, showing both historical and current distribution patterns across disease types while accounting for NBS results. Motor abilities of children detected through NBS program are presented through motor function assessment scores and electrophysiological measurements (CMAP) as these children can't be classified within the traditional SMA types. Since the implementation of NBS, we have identified several children with multiple copies of the ***SMN2*** gene (4 to 6 copies) who would likely remain asymptomatic for a long time. These data provide a foundation for the assessment and treatment planning amid emerging therapeutic options.

P153

A national action plan dedicated to emergencies DRIVEN by the French association AFM-Téléthon

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Since the 2000s, the AFM-Téléthon association anticipated these needs by creating tools like the « Care and emergency card for neuromuscular diseases ». Faced with the recurrence of serious errors in emergency situations, the association launched a national action plan in 2013 aimed at informing all the stakeholders (patients and families, healthcare professionals, health authorities) as well as structuring and coordinating the care of each patient.

P155 - FLASH TALK

The Natural History of SMA with Four SMN2 Copies: Evidence from the Spanish Registry (CUIDAME)

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Spinal muscular atrophy (SMA) is caused by homozygous deletions or mutations in the SMN1 gene, with disease severity influenced by the number of SMN2 gene copies. Individuals with 4 copies of the SMN2 gene copies are generally considered to present with milder phenotypes, yet their long-term progression is still not fully understood. The phenotypic variability in those patients remains a challenge for prognosis and clinical management.

We analyzed the natural history from 84 SMA patients, focusing on age of onset, acquisition and loss of motor milestones (sitting, standing, walking), and associated complications, before the onset of disease modifying therapies. All data were issued from Spanish national registry of SMA patients (CUIDAME).

Our cohort included 34 females (40.5%) and 50 males (59.5%). Symptom onset occurred at median of 38 months [IQR 17.75, 144]. All patients achieved the ability to sit, 90% were able to stand, and 88% acquired independent walking. Overall, 12% of patients with 4 copies of SMN2 were classified as SMA type2, 83% as SMA type 3 and 5% as SMA type 4. At a median age of 37.5 years at the end of follow up [IQR 22.9, 47.75], 38% of patients had lost the ability to walk. Moreover, 35% had also lost the ability to stand and 5% the ability to sit. Wheelchair use was reported in 46% of patients, scoliosis in 32%, and need for non-invasive ventilation in 12%. No patient required nutritional support.

Our findings highlight that patients with 4 SMN2 copies experience functional decline and, in some cases, severe complications across their lifetime. This has important implications for newborn screening (NBS) programs and therapeutic decision-making, as presymptomatic treatment in individuals with four SMN2 copies remains under debate. Our data, consistent with other reports, underscore the need for tailored follow-up protocols and careful consideration of treatment timing following NBS identification.

P157

Bones under pressure: A multi-centre retrospective study of bone health in adults with spinal muscular atrophy

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Spinal muscular atrophy (SMA) is a genetic neuromuscular disorder characterised by degeneration of motor neurons, resulting in progressive muscle weakness, functional decline, and early loss of ambulation. While advances in disease-modifying therapies have improved survival, secondary complications remain a major contributor to morbidity. Bone health represents an important, and potentially modifiable, determinant of long-term outcome in SMA. Impaired bone health increases fracture risk, which in turn accelerates functional decline. The pathogenesis of poor bone health in SMA is thought to be multifactorial, arising from chronic muscle weakness, reduced weight-bearing activity during critical periods of growth, and potential direct effects of survival motor neuron protein deficiency on bone metabolism.

In this study, we analyse bone health parameters from a large multi-centre cohort of adults with SMA to characterise the prevalence and risk factors of bone health impairment in this population.

This retrospective study included adults with SMA managed at four neuromuscular centres in the UK. Data on demographics, clinical characteristics, biochemical bone health markers, dual-energy X-ray absorptiometry (DXA) findings, fracture history, and bone health management were collected from clinical records using a standardized tool. Univariable and multivariable binary logistic regression analyses were used to evaluate associations of low bone mineral density (BMD), fracture history, and vitamin D deficiency.

A total of 233 adults with SMA were included (median age 32 years, IQR 24-44, range 17-78). 55.4% (n=129) had SMA type 3, 42.1% (n=98) type 2, 1.7% (n=4) type 1, and 0.9% (n=2) type 4. Approximately one-third of the cohort (35.2%) had undergone DXA scanning, the majority of whom were individuals with SMA type 3 (n=53). Among those who underwent DXA, two-thirds (76.3%) had low/borderline low BMD. Ambulatory status was independently associated with low BMD, with non-walkers having nearly fourfold higher odds of low BMD compared with walkers (adjusted OR [aOR] 4.17, 95% CI 1.07-16.7, $p = 0.039$). One-third of the cohort (29.2%) reported a history of fracture. Walkers had nearly twice the odds of reporting a previous fracture compared with non-walkers (aOR 1.98, 95% CI 1.01–3.89, $p = 0.046$). Low vitamin D status was also independently associated with fracture history (aOR 0.99, 95% CI 0.97–0.999, $p = 0.041$). Low vitamin D levels were found in two-thirds of the cohort (64.7%) with a disproportionately higher prevalence among non-White individuals ($p < 0.001$).

Early bone protective strategies are required to address bone fragility in adults with SMA with emphasis on maintaining weight-bearing function where feasible and the use of resistive exercises, falls prevention strategies, and individualised vitamin D dosing. This study also highlights practical limitations of DXA BMD measurement in this population.

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Real-life outcome data on Risdiplam therapy for Spinal Muscular Atrophy

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Risdiplam is an orally administered novel small molecule approved for the treatment of spinal muscular atrophy (SMA), a rare and debilitating neuromuscular disorder. Risdiplam acts as a survival motor neuron (SMN) 2 splicing modifier, promoting the production of functional SMN protein, which is crucial for motor neuron survival and function. By increasing SMN protein levels, risdiplam compensates for the deficiency caused by SMN1 gene mutations, the underlying genetic cause of SMA.

We collected the clinical outcome data of all individuals with SMA treated with risdiplam at the SMA clinic in a large tertiary hospital.

The study participants included 22 individuals who received risdiplam between 5 months and 24 years of age (median age 15 years, interquartile range [IQR] 12-21) and whose median follow-up duration was 16 ([IQR] 9.3-19.1) months. Of these patients, 18 were previously treated with intrathecal nusinersen and 4 patients were treatment naive.
Compared to baseline, in SMA type 1 patients, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scores were stable or slightly increased by a median of 0.4 points at last follow-up, while in SMA types 2-3 patients Hammersmith Functional Motor Scale Expanded (HFMSE) scores showed a mild increase by a median of 2 points at last follow-up and Revised Upper Limb Module (RULM) scores showed an increase of 1 point. No changes in ventilatory status or bulbar function were noted during risdiplam follow-up. Five out of 22 patients had mild adverse effects, including headache, vomiting, nausea and rash which resolved within days.
Overall, risdiplam was well tolerated, easy to handle and led to stable or slightly improved motor function outcomes in SMA patients.

P161

Evolving phenotypes and ventilation needs in SMA in the post-treatment era: Results from a European community survey

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Spinal muscular atrophy (SMA) is a progressive, degenerative neuromuscular condition that is characterised by significant phenotypic variability. With the advent of disease-modifying treatments (DMTs), earlier diagnosis and improved standards of care, this heterogeneity has increased further, resulting in disease trajectories and phenotypes that no longer fit the traditional type-based classifications of SMA. Evolving phenotypes have been well described in the motor domain. Respiratory function, and in particular ventilation need, despite being used as a criterion for DMT reimbursement, has received less attention. The aim of this study was to explore respiratory phenotypes in the era of DMTs.

We analysed data from SMA Europe's 2025 community survey (N=826). Participants were categorised based on ventilatory status: no ventilation (n=519), non-invasive ventilation (NIV) <16 hours/day (n=205) or ≥16 hours/day(n=15), and tracheostomy <16 hours ventilation/day (n=11) or ≥16 hours ventilation/day (n=31). Demographic and clinical characteristics, as well as experiences with DMT were explored to identify features of respiratory groups.

The "no ventilation group" included mainly individuals with less severe motor phenotypes (sitters: 47.4%; walkers: 26.0%), while the tracheostomy groups had the highest percentage of individuals living with more severe phenotypes (non-sitters: 55.6% and 93.5% in the <16 and ≥16 hours/day groups, respectively). Nevertheless, all groups included non-sitters, sitters and walkers, reflecting heterogeneity in motor function across the respiratory continuum.

Among respondents receiving DMTs, the majority in all groups reported improvement or stabilisation across different domains since starting treatment: respiratory function (96.0%), fine motor skills (94.7%), muscle strength (90.2%), endurance (92.3%), fatigue (90.0%), speaking (99.1%), eating (96.9%), fractures (97.9%) and respiratory infections (96.3%). There were no meaningful differences observed between groups.
Within the tracheostomy groups, the most frequent reasons for tracheostomy placement were clinician recommendation, difficulties with extubating, frequent respiratory infections, and the need for more stable ventilation and efficient airway clearance. Most of these participants reported fewer hospitalisations and improvements in both quality of life and sleep following tracheostomy.

These results confirm that increased respiratory needs, including the use of tracheostomy, are more common in severe motor phenotypes, while also demonstrating heterogeneity in motor function across the respiratory continuum. They further show that individuals living with the most severe respiratory needs can benefit from both tracheostomy and DMTs across multiple domains extending beyond motor and respiratory function. Together, these results emphasise the importance of guiding SMA treatment and care decisions by clinical, functional and psychosocial outcomes, and support a more holistic and equitable approach to understanding and managing SMA.

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European patient experience survey in SMA (EUPESMA 2025): Treatment access, perceptions, and future needs

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Spinal muscular atrophy (SMA) has undergone a paradigm shift since the European Medicines Agency approved the first disease-modifying therapy (DMT) in 2017. Today, three DMTs are available, with additional therapies in development, offering unprecedented options but also creating a complex and evolving treatment landscape. Although access has expanded, it remains uneven across countries and patient groups, shaping treatment experiences and decision-making, and leaving important unmet needs. SMA Europe conducted EUPESMA 2025 (European Patient Experience Survey in SMA), a biennial pan-European survey designed to systematically capture the perspectives of people living with SMA and their families.

The survey was available in 18 languages as an online questionnaire distributed through SMA Europe and its 30 member organisations. A total of 826 individuals from 41 countries participated. Mean age was 28 years (SD = 18.9), 56.6% reported being assigned female at birth. Respondents were people living with SMA (58.8%), legal guardians (39.5%), or others (1.7%).

Treatment access and uptake. Of all respondents, 58.0% (n=478) had been diagnosed before the availability of SMA clinical trials or DMTs. At the time of the survey, 85.5% (n=694) had received at least one treatment, and 7.7% (n=64) were enrolled in a clinical trial. Among those on therapy, 135 (21%) had switched treatments (from one DMT to another), most often due to mode of administration (n=87), side effects (n=18), hope to see more improvement (n=19), or opportunity to try a new option (n=23). Among respondents receiving a single-dose therapy, 38 (40.0%) had previously received a DMT and 17 (17.9%) received one afterward.

Decision-making and perceptions. Overall, 554 patients (85.5%) reported having had sufficient information to decide on treatment initiation. However, 177 (27.5%) still considered the decision difficult due to insufficient safety and efficacy evidence. Treatment was perceived as both taking a risk (40.6%, n=260) and having an opportunity (85.3%, n = 546). Only 197 (30.7%) reported having a choice of initial treatment, and 184 (29.3%) reported being able to switch.

Patient-reported outcomes and satisfaction. Only 64 treated respondents (9.3%) indicated that their treatment expectations had not been met at all. Most reported stabilisation or improvement across multiple domains, including fine and gross motor function, muscle strength, respiratory and bulbar function, and weight. Importantly, 710 patients (89.6%) considered stabilisation itself as progress.

Future needs. Despite high overall satisfaction, 641 respondents (82.3%) expressed the need for additional SMA medicines, 143 (17.1%) were unsure, and 5 (0.6%) reported no need. Priorities for future therapies included muscle rebuilding/strengthening (89.2%, n = 702) and motor neuron regeneration/health (86.7%, n = 682). Willingness to participate in clinical trials was high, with 558 patients (71.1%) responding positively, 170 (21.7%) undecided, and 57 (7.3%) declining.

Most people living with SMA in Europe are now receiving treatment and report satisfaction, particularly valuing stabilisation as meaningful progress. Yet many also express the wish for therapies that could deliver further improvement, underlining that significant unmet needs remain. Disparities in access, choice, and switching opportunities highlight persistent equity gaps across and beyond Europe. At the same time, the strong call for new medicines, especially those targeting muscle rebuilding and motor neuron regeneration, together with the high willingness to participate in clinical trials, underscores both the urgency of advancing new solutions and the global engagement of the SMA community to shape the next generation of research.

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OdySMA – Tracking access to SMA treatment and care through quantitative and qualitative data

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SMA Europe, the umbrella organisation of spinal muscular atrophy (SMA) patient groups across Europe, aims to improve access to diagnosis, optimal treatment and care for all individuals living with SMA. ***OdySMA - a quest to access*** is SMA Europe's participatory initiative to systematically identify and monitor barriers to access, providing evidence to advocates and stakeholders so that no one is left behind.

OdySMA profiles 26 countries across 21 datasets, covering diagnostics, therapy access, care infrastructure, policy frameworks, and adult care. Quantitative indicators are continuously updated through structured feedback from national patient organisations and other stakeholders, and visualised in an interactive atlas and the comparative "Nations League." Complementing this, OdySMA collects qualitative data through in-depth interviews and collaborative storytelling, making visible the lived impact of access inequities.

Findings to date show persistent disparities across Europe. Access to medicines varies by country and across the SMA spectrum, while newborn screening implementation differs both between and within countries. A benchmarking report on adult SMA care identified a pressing need for updated international standards. Real-life Stories illustrate the consequences of inequitable access: for example, receiving treatment can enable individuals to plan for the future, while others are excluded based on factors beyond their control, such as age or tracheostomy status.
By combining rigorous benchmarking with lived experiences, OdySMA transforms data into an advocacy tool. It provides a complex and evolving picture of access in Europe while offering a public platform to the voices of people with SMA. This dual approach equips stakeholders with the evidence and narratives needed to drive urgent, equitable solutions.

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System-level barriers, reimbursement gaps, and crowdfunding: insights from the SMA Europe member survey

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The approval of three disease-modifying therapies (DMTs), all designated as orphan drugs, has transformed the therapeutic landscape for spinal muscular atrophy (SMA), altering its trajectory by slowing or stabilising progression and, in some cases, restoring function. However, high treatment costs and exclusionary reimbursement criteria, often tied to type-based classifications and rigid cut-offs such as age, mobility, ventilation status, or SMN2 copy number—continue to limit access in many countries. For families excluded by such criteria, lack of access often leads to despair and drives them towards alternatives outside the public system. In this context, medical crowdfunding has emerged as a last resort, raising profound ethical and social concerns. To better understand these challenges, SMA Europe investigated reimbursement structures and the role of crowdfunding.

An online Member Survey (2024) was distributed to all SMA Europe member organisations, targeting system-level perspectives on access. Responses were received from 21 representatives across 18 European countries. Findings were further explored in a dedicated face-to-face workshop in June 2024, where patient organisations contextualised the survey data and shared country-specific access challenges. This mixed approach integrated structured survey data with qualitative insights, capturing not only policy gaps but also their real-world consequences.

Findings revealed three main themes:

- Reimbursement gaps: Despite major advances in the regulatory approval of DMTs, followed by national reimbursement negotiations, a persistent disconnect between policy decisions and real-world access was reported. Policies on switching, combining, or bridging therapies were described as fragmented and restrictive, reflecting inequities highlighted in OdySMA's Nations League benchmarking and aligning with patient-reported barriers in the EUPESMA survey.

- Crowdfunding as a symptom of inequity: Medical crowdfunding has emerged as a last resort when formal access pathways fail, reflecting systemic shortcomings rather than true patient choice. Families turn to it out of desperation, but it plays on the hopes of the most vulnerable, exposes them to misinformation and exploitation by fundraising platforms, and risks devastating financial loss. Crowdfunding thus highlights individual distress while underscoring the urgent need for robust, equitable public access systems.

- Information needs: Respondents highlighted an urgent need for accurate, accessible information on SMA therapies to counter misinformation and support informed, collaborative treatment choices.

Such barriers not only create inequities but also delay treatment initiation, which is clinically critical in a progressive disease such as SMA. Moreover, rigid frameworks tied to type classifications fail to reflect the continuum of abilities and multisystem domains of SMA, excluding individuals whose trajectories do not fit neatly into predefined categories.

System-level barriers continue to constrain equitable access to DMTs across Europe. Crowdfunding makes these failures visible: it is a symptom of systemic shortcomings, not a solution, and it amplifies family vulnerability. Addressing these barriers requires collective responsibility: governments and payers must ensure transparent and inclusive reimbursement frameworks; industry should engage in equitable pricing and access solutions; healthcare professionals must support evidence-based decisions; and patient organisations must provide data and advocate for equity. Through its coordinated member network, SMA Europe contributes by challenging exclusionary criteria and complementing OdySMA's system-level monitoring. Together, these efforts are essential to advance the shared goal that no one is left behind.

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Temporal SMN2 modulation restores motor function in SMA organoids via ciliary gene rescue

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Spinal muscular atrophy (SMA) represents a severe neurodegenerative disorder caused by survival motor neuron (SMN) protein deficiency, leading to progressive motor neuron degeneration. Despite advances in SMN-restoring therapies, treatment timing remains critical yet poorly understood. We developed patient-derived spinal cord organoids using a novel Matrigel-free protocol to investigate temporal dynamics of therapeutic intervention and uncover disease mechanisms. Our model recapitulated key SMA pathological features including altered GABAergic neuron morphology, enhanced astrogliosis, and disrupted electrical network activity measured through multielectrode array recordings, providing a physiologically relevant platform for therapeutic evaluation.

We discovered widespread ciliary gene dysregulation as an unexpected hallmark of SMA pathogenesis. RNA sequencing revealed significant downregulation of essential ciliary structural components and transition zone proteins, suggesting compromised cellular signaling and transport mechanisms. Treatment with RO7021707, a next-generation SMN2 splicing modifier similar to Risdiplam, demonstrated striking temporal dependency. Optimal therapeutic efficacy occurred when treatment began at differentiation day 45, achieving maximal SMN protein restoration and functional network recovery. Earlier or later intervention showed substantially reduced benefits, highlighting a critical therapeutic window.
Organoids enable temporal mapping of therapeutic windows and disease mechanisms critical for precision medicine in SMA.

P171

Evaluating the therapeutic potential of fluphenazine on the neuromuscular phenotype in Spinal Muscular Atrophy

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Spinal muscular atrophy (SMA) is a degenerative neuromuscular disorder caused by the loss or mutation of the ***survival motor neuron 1 gene*** (***SMN1***), which renders the gene dysfunctional. This results in depletion of its product, the ubiquitously expressed SMN protein. The SMN protein is vital for the survival of motor neurons, and its depletion leads to progressive muscle atrophy, and in its most severe forms, infant mortality. Most recent advancements in drug development have resulted in three SMN-dependent gene therapies. However, none of these therapies offer a cure. Consideration of additional complementary treatments targeting dysfunctional SMN-independent pathways is merited. Autophagy, a highly conserved lysosomal-degradation pathway essential for cell homeostasis and neuronal survival, is reported as dysregulated in SMA. Compounds that target this pathway may offer an insight into the role autophagy plays in SMA pathogenesis and identify its potential as a therapeutic target. Our unpublished work in the ***Caenorhabditis elegans*** (***C. elegans***) SMA model has demonstrated that fluphenazine, an autophagy modulator and dopamine receptor antagonist, improves several key phenotypes in the ***C. elegans*** SMA model. In this study, we expanded this work utilising the intermediate $Smn^{2B/-}$ SMA mouse model to assess the therapeutic potential of fluphenazine. Our molecular analyses using brain, spinal cord and skeletal muscle tissue at different time-points demonstrated that both autophagy and dopaminergic pathways are aberrantly regulated in the $Smn^{2B/-}$ model in a tissue- and disease stage-dependent manner. Although fluphenazine did not improve the phenotype of the $Smn^{2B/-}$ mouse model, treatment was able to modulate molecular markers of autophagy and alter the expression of specific dopamine receptors. Furthermore, fluphenazine induced a downregulation of the transcription factor ***FoxO1***, a key upstream regulator of autophagy. Finally, fluphenazine was able to influence motor neuron properties in a disease-specific manner. Overall, our study contributes to the growing body of evidence demonstrating that autophagy and dopamine signalling are disrupted in SMA.

P173 - FLASH TALK

Beyond spinal motor neurons: Cortical projection neuron numerical and morphological alterations reveal selective vulnerability to SMN loss also in the brain

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Spinal Muscular Atrophy (SMA) has long been recognized as a motor neuron disease, since the lack of survival motor neuron (SMN) protein was shown to primarily drive the degeneration of spinal motor neurons and the resulting motor phenotype. However, growing evidence from both patients and animal models indicates that cortical neurons are also affected, suggesting a broader and more complex neurodegenerative process.

In this work, we investigated the sensorimotor cortex of SMAΔ7 mice, a severe SMA model, to evaluate the impact of SMN deficiency on cortical projection neuron (cPN) survival, morphology, and development. We investigated the SMAΔ7 sensorimotor cortex at early (P5) and late (P11) symptomatic stages using immunofluorescence, retrograde tracing, and thymidine analogue labeling. At P11, we observed a significant loss of layer V projection neurons, with corticospinal (Ctip2-positive) and callosal (Satb2-positive) populations reduced by ~50% and ~36%, respectively. Strikingly, these neurons displayed marked morphological alterations, including reduced soma size, impaired dendritic arborization, and decreased dendritic spine maturation. Some of these structural defects were already detectable at P5, suggesting that certain cPN populations, especially the corticospinal one, are more vulnerable to SMN deficiency from the earliest stages of disease. In contrast, corticothalamic neurons appeared to be relatively spared, supporting the idea that SMN deficiency does not uniformly affect all cPN subtypes. In addition, preliminary developmental analyses revealed altered distribution of neurons born at embryonic days E14–E15, indicating that SMN deficiency influences cortical layering and cytoarchitecture during corticogenesis. This developmental misplacement may represent an early event that predisposes cPNs to subsequent degeneration. Together, our findings highlight that not all cortical neurons are equally affected: corticospinal and then callosal projection neurons emerge as particularly vulnerable populations, displaying both structural and survival deficits in response to SMN reduction.

By highlighting the morphological impairments and differential susceptibility of cortical neurons, our study broadens the view of SMA pathogenesis. Understanding how cortical projection neurons are selectively compromised provides novel insights into disease progression and may guide therapeutic strategies aimed at preserving cortical integrity and enhancing motor and cognitive outcomes in SMA.

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Genetic Insights into SMA: Beyond copy number to modifiers and cohort screening

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Spinal Muscular Atrophy (SMA) is a rare neuromuscular disease caused by biallelic mutations of ***SMN1***. SMN levels in patients depend on ***SMN2*** copies, which usually inversely correlates with disease severity, yet discordant cases highlight modifier effects, prompting investigation of the genetic background in 71 patients from 58 Turkish SMA families.

To explore genotype-phenotype correlations, ***SMN1*** and ***SMN2*** copy numbers, along with ***NAIP*** exon 5 were quantified by MLPA. WES was performed to assess candidate modifiers and potential dual diagnoses. PCR-RFLP was applied in patients with reduced ***GTF2H2*** coverage in WES to detect extended deletions. In a parallel analysis, NDAL WGS and WES cohorts were screened with SMNCopyNumberCaller and SMA Finder, respectively.

Our SMA cohort consists of 71 patients (Type I: 10, Type II: 14, Type III: 44, Type IV: 3); the majority had homozygous ***SMN1*** exon 7–8 deletion, while seven patients carried hybrid SMN genes. One patient was a compound heterozygote of ***SMN1*** exon 7–8 deletion and p.Leu228Ter. All parents had a single ***SMN1*** copy except for two unrelated mothers with two ***SMN1*** copies who are potential silent carriers. Most frequent ***SMN2*** copies were 2, 3, 3-4, and 4 in types I, II, III, and IV, respectively. The highest frequency of ***NAIP*** homozygous deletion was in Type I patients and homozygous deletion of ***GTF2H2*** exon 10 was observed in three Type I cases. WES revealed the ***SMN2*** positive modifier (c.859G>C) in two Type III patients with 2 and 3 ***SMN2*** copies. Notably, the patient with 2 ***SMN2*** copies who was homozygous for the variant showed a milder phenotype than expected. This patient also exhibited a milder course than the Type III patient with 3 ***SMN2*** copies carrying the heterozygous variant. In another case who had epilepsy in the neonatal period, WES suggested a dual diagnosis upon the identification of a heterozygous reported variant (c.1632-1G>A) in the ***KCNQ2*** gene. Through cohort-wide analyses, i) carrier frequency was assessed as 2.7% (n=1056) in the WGS cohort, and ii) a patient with MND clinical diagnosis in the WES cohort was found to have SMA, later validated by MLPA. This case holds particular significance for precise diagnosis, especially in the treatment era.

To the best of our knowledge, this study represents the first comprehensive work in Türkiye combining diverse methods and objectives. Our findings shed light on genotype–phenotype correlations and highlight silent carriers among SMA parents, carrier frequency in the WGS cohort, and the importance of uncovering SMA cases previously attributed to other diagnoses. These results may facilitate the adoption of similar strategies in research laboratories to identify SMA cases previously unrecognized. With the advent of effective therapies, SMA has become a hopeful disease, and sustained collective efforts have the potential to further transform a condition once considered among the cruelest.

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Targeting autophagy partially rescues neuromuscular function and extends lifespan in a *C. elegans* model of Spinal Muscular Atrophy

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Spinal muscular atrophy (SMA) is a severe neuromuscular disorder caused by reduced levels of the ubiquitously expressed survival motor neuron (SMN) protein, leading to degeneration of lower -motor neurons, progressive muscle atrophy and infant mortality. Although SMN deficiency is systemic, the mechanisms underlying selective motor neuron vulnerability remain incompletely understood. Previous SMA mammalian and cell culture studies have reported dysregulation of autophagy, a highly conserved lysosomal degradation pathway vital for neuronal survival. However, it remains controversial whether the pathway successfully progresses to its endpoint or is impaired following initiation.

To identify the specific stage at which autophagy is perturbed, we used the well-established ***Caenorhabditis elegans (C. elegans)*** SMA model. Transcriptomic analysis revealed a broad upregulation of autophagy-associated genes, but this was accompanied by reduced lysosomal biogenesis and acidification, indicative of defects in the latter stages of the pathway. Consistent with this, fluorescent reporter assays demonstrated an accumulation of autolysosomes which were likely to be non-degradative, while p62 levels were elevated, supporting a block in autophagic turnover.

To explore whether modulation of autophagy could be therapeutically beneficial, we next investigated the effects of various autophagy activators and inhibitors. Autophagy activators such as rapamycin, resveratrol, torin-1 and fluphenazine significantly improved neuromuscular performance. Strikingly, these effects were also observed in an alternative severe C. elegans SMA model and persisted under conditions of metabolically inactive food, demonstrating robustness across genetic and dietary backgrounds. Moreover, autophagy activators were capable of increasing endogenous SMN levels and extend the lifespan in SMA nematodes, without detectable impact on heterozygous controls. In contrast, four autophagy inhibitors failed to improve neuromuscular defects.

Collectively, our findings demonstrate that impaired autophagic degradation is a key feature of SMA pathology in C. elegans and show that pharmacological activation - but not inhibition - of autophagy ameliorates core disease phenotypes.

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Two-year efficacy and safety of risdiplam treatment in adult patients with Spinal Muscular Atrophy: Motor, respiratory, and patient-reported outcomes

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Spinal muscular atrophy (SMA) is a rare, autosomal recessive neuromuscular disorder characterized by progressive muscle weakness and atrophy. Advances in the understanding of its underlying pathophysiology have enabled the development of disease-modifying therapies. Risdiplam (Evrysdi®), an orally administered SMN2 splicing modifier, has demonstrated efficacy in paediatric populations. However, evidence regarding the long-term use in adults remains limited.
Objectives: To evaluate the efficacy of Risdiplam treatment on clinical, functional, and patient-reported outcome measures (PROMs), as well as the safety and tolerability, in adults with SMA types 2, 3, or 4 over 24 months.

Eighteen treatment-naïve adults with SMA types 2, 3, or 4 received Risdiplam treatment for 24 months. Motor and strength outcomes included manual muscle testing, hand grip key and pinch strength, the Motor Function Measure-32 (MFM-32), and the Revised Upper Limb Module (RULM). Swallowing was assessed using the Functional Oral Intake Scale and the Neuromuscular Disease Swallowing Status Scale. PROMs included the SF-36 quality of life scale, Fatigue Severity Scale, Sydney Swallow Questionnaire, and SMA Independence Scale. Respiratory function was evaluated by the forced vital capacity (FVC) and peak expiratory flow (PEF). In the absence of a control group, retrospective pulmonary data from up to five years prior to treatment initiation of the included patients were analysed for comparison.

The MFM-32 scores increased significantly at 12 months (+2.3%) and 24 months (+2.6%; both $p < 0.01$). Additionally, the RULM improved significantly at 12 months (+1 point; $p = 0.02$). The FVC remained stable, deviating from the annual decline observed in the retrospective analysis, while the PEF improved significantly after 24 months (+6.9%; $p = 0.03$). Quality of life improved, and significant reductions were found in fatigue and dysphagia after 12 months (-3.5 points, $p=0.03$; -4 points, $p=0.01$, respectively) and 24 months (-5.8 points, $p<0.01$; -5.6 points, $p<0.01$, respectively). Risdiplam was generally well tolerated, with a favourable safety profile.

In adults with SMA, two years of Risdiplam treatment resulted in significant improvements in motor function, quality of life, fatigue, and dysphagia. Moreover, stabilization of the respiratory function was observed. Risdiplam demonstrated a favourable safety and tolerability profile, supporting its long-term therapeutic utility in the adult SMA population.

P181

The ACE SMA study: 18-month single site, acceptability, feasibility, safety and efficacy data of an optimised rehabilitation program for treated patients with SMA in the United Kingdom

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The current treatment landscape for spinal muscular atrophy (SMA) is rapidly evolving with several approved disease modifying therapies showing efficacy across the disease spectrum. To optimise the impact of treatments, current standards of care highlight the importance of a multidisciplinary team with increased physiotherapy. Specifically, in regards to rehabilitation there is increasing evidence for a proactive individualised approach including access to regular sessions of physiotherapy. As demonstrated in a UK national survey in 2022, 57% of paediatric patients living with SMA would be more satisfied with increased frequency of access to a physiotherapist. And subsequently, only around 65% of the participants are seen once or twice a year. Furthermore, patients and caregivers rated the importance of various interventions, with mobility and stretching as most important followed by strengthening exercises. Emphasising the need for access to rehabilitative physiotherapy among the SMA population.

With this knowledge, we are conducting an acceptability, feasibility, safety and exploratory efficacy study (titled ACE SMA) of an individualised, optimised, rehabilitation program. To quantify and assess the uptake of physiotherapy among a sample size of 14 treated patients living with SMA up to 10 years of age from study inclusion. The study administers, once every two weeks, hands-on physiotherapy sessions and weekly home-use of a rehabilitation device over a period of 18 months. Motor function outcomes are assessed at baseline, month 6, month 12 and month 18. Month 18 comprises of a 6-month study extension that was approved by the ethics committee in Q1, 2025.

At 6 months, the ACE SMA study showed 93% acceptability and 100% feasibility (no dropouts) among eligible participants (n=10). 90% were likely to recommend the hands-on physiotherapy and device use, and all were satisfied with the care compared to NHS services. Additionally, 70% found the program easy to integrate into daily life, and no serious adverse events were reported. At the congress we will present the 12-month data (n= 13) of the ACE SMA study alongside exploratory efficacy data.

The ACE SMA study, intends to provide a proof of concept for the uptake of frequent and optimised physiotherapy in patients living with SMA to inform the conduct and implementation of late-phase multi-centre efficacy studies. These future studies may support the integration of more regular and personalised physiotherapy into standard care pathways of SMA patients within the UK.

Current standards of care within spinal muscular atrophy (SMA) highlight the importance of increased physiotherapy and proactive individualised rehabilitation alongside treatment. Yet in the UK, a survey in 2022 highlighted a large unmet need of regular physiotherapy.

The ACE SMA study aims to determine if more frequent and individualised physiotherapy is up taken and is feasible by patients living with SMA and their families in the UK. The study provides 14 patients living with SMA, hands-on physiotherapy sessions every two weeks with the use of a rehabilitation device at home over 18-months. 6-month results show that 93% accepted to participate, 100% completed their 6-month visit and 90% would recommend the individualised program.

We aim to present the 12-month data of 13 patients alongside safety, effectiveness and compliancy data. The ACE SMA study hopes to provide a concept for regular optimised physiotherapy to support integration into SMA standard of care pathways in the UK.

P183

Understanding neurologist perspectives on the clinical meaningfulness of 'any point differences' on the Hammersmith Functional Motor Scale-expanded in SMA

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Spinal muscular atrophy (SMA) is a severe neuromuscular disease characterized by the irreversible loss of spinal motor neurons and progressive skeletal muscle atrophy and weakness, leading to motor function decline. SMA treatment efficacy is traditionally measured by motor function assessments (eg, HSMSE, MFM-32); however, treatment impact on clinically meaningful change is difficult to ascertain and usually requires additional insights from patients or their caregivers.
To better understand existing perspectives on the clinical meaningfulness of functional changes within the HFMSE, we conducted 60-minute semi-structured interviews among patients and their caregivers, as well as providers (neurologists/physical therapists) experienced with treating SMA and utilizing the HFMSE to monitor motor function.

Here we report results from 11 interviews with neurologists, focusing on their interpretation of what constitutes clinically meaningful change for the HFMSE and functional tasks that may be the most meaningful.

For neurologists, the most common clinical settings of practice were universities/academic medical centers (4/11; 36.4%) and multi-specialty group practices (3/11; 27.3%). All 11 neurologists (100%) reported they spend at least 80% of their work week treating patients. Additionally, all neurologists indicated they were 'very familiar' with the HFMSE (100%), with 10 (90.9%) reporting they received training on its administration. When asked to define clinically meaningful change, neurologists often took a patient-centered approach, describing it as a shift that noticeably improves a patient's functioning, independence, and ability to carry out activities of daily living. They emphasized that any point improvement across functional tasks within the HFMSE represents meaningful indicators of independence and quality of life, especially if the patient could not perform these tasks previously. One neurologist emphasized this when discussing the lifting hand to head task, "They [patients] would have more autonomy…This means that they can do certain tasks better such as feeding themselves…" Another neurologist expressed similar sentiments for improving in the standing task, "Standing alone, you can probably take a shower that way by yourself, dress by yourself. That's big."
Based on neurologists' responses, clinically meaningful change is best understood through a patient-centered lens, where improvements in daily function and independence are evaluated in the context of individual goals and lived experience. Neurologists agreed that any point improvement, regardless of functional task, can reflect significant impacts on patients' independence and quality of life, underscoring the clinical and patient-centric importance of measuring and charting small changes.

P185

Respiratory outcome in patients with spinal muscular atrophy treated with disease modifying therapies: A real-life multicenter study in Belgium

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Spinal muscular atrophy (SMA) is a rare neuromuscular disorder characterized by progressive muscle atrophy and weakness, also affecting respiratory function in more severe cases. Disease-modifying therapies (DMT) - nusinersen, onasemnogene abeparvovec, and risdiplam - have significantly altered survival and motor outcomes across the different SMA types, particularly when initiated presymptomatically. However, the impact of DMT on respiratory function is still poorly evaluated and the available real-world data are conflicting.

To evaluate changes in lung function trajectories and ventilation requirements in SMA type 2 and 3 patients during the first years of treatment with DMT.
Methods: We conducted a longitudinal study (2018–2024) using the Belgian Neuromuscular Disease Registry (BNMDR) SMA, which annually collects standardized data across all Belgian neuromuscular reference centres. Eligible patients had genetically confirmed SMA type 2 and 3, resided in Belgium, and consented to registry participation.
For the analysis involving spirometry measurements, we included patients with available baseline forced vital capacity (FVC, in mL and %pred) at treatment initiation, and ≥2 follow-up FVC measurements obtained during routine clinic visits. Patients who switched DMT were excluded from this analysis. Annual FVC decline rates were calculated, per SMA type and for nusinersen and risdiplam separately. Given recent evidence in literature of age-related patterns of lung function decline in non-treated SMA patients, we divided patients in age-specific groups accordingly.

The registry included 336 SMA patients at time of analysis, of which 247 patients with type 2 and 3. Among those, after applying the selection criteria cited above, we analysed 74 with SMA type 2 and 70 with SMA type 3. Age at start of treatment in SMA type 2 was distributed as follows: 14.3% before 5 y, 20.4% between 5-14 y and 65.3% after 14y. In SMA type 3, treatment was received mainly after 14 y (86.5%) or between 5-14 y (13.5%). Annual decline in FVC %pred in SMA type 2 treated with nusinersen (n=6) was -3.82% in the 5-14 y age group and +0.15% in the age group >14y. In patients treated with risdiplam (n=17), the annual decline rate was -1.27% in the 5-14 y age group and -1.13% in the patients >14y. In SMA type 3, the annual decline in FVC %pred was +0.40% in patients >14y with nusinersen (n=13) and -0.07% in patients >14y with risdiplam (n=10). Our findings suggest that treatment may slow down lung decline in patients who received DMT, compared with natural history cohorts. Ventilatory requirement data are expected to be available soon.

This multicentre study provides the first real-life longitudinal data on respiratory outcome in Belgian patients with SMA treated with DMT. The natural history of respiratory function decline may be modified by DMT in SMA type 2 and 3, thereby guiding clinical management and long-term follow-up strategies.

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Changes of activities of daily living among adults living with SMA - A cross-sectional analysis from the Cure SMA annual community update survey

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Real-world data has shown early treatment with disease modifying therapies (DMTs) is correlated with gains in motor milestones in those affected with spinal muscular atrophy (SMA). However, individuals receiving a DMT much later in their disease progression may experience less clinically significant changes in motor milestones. Evaluating different outcomes, such as ability to perform activities of daily living (ADLs) may be a more appropriate measure of treatment response in those treated later in life.

The Cure SMA Community Update Survey (CUS) has been collecting data on the lived experiences of people living with SMA since 2017. The objective of this analysis is to evaluate changes in ADLs over the previous 12 months among adults living with SMA utilizing the 2025 CUS.

449 surveys were completed for 433 unique individuals between April 24 and May 26, 2025. Final sample included 184 adults living with 5q SMA (individuals deceased, <18 years old at time of survey, or missing DMT dates were excluded). 154 individuals were receiving a DMT for ≥12 months prior to the survey (treated group). All in treated group were on a single DMT at time of survey. 30 individuals had not been treated with a DMT over the previous 12 months. Of these, 18 discontinued treatment ≥ 12 months ago (discontinued group), and 12 had never been treated with a DMT (untreated group). 47.4% had SMA type 2 or 3 in the treated group. 61.1% and 58.3% had SMA type 2 in the discontinued and untreated groups, respectively. The mean(s.d.) age, in years, at the time of survey was 38.1(13.7), 38.8(9.5), and 46.8(15.7) for the treated, discontinued, and untreated groups, respectively. The mean(s.d.) age at SMA diagnosis, in years, was 6.4(10.1), 5.3(8.4) and 15(16.3) for the treated, discontinued, and untreated groups, respectively. The mean(s.d.) time on treatment, in years, was 5.7(1.9) and 2.1(1.8) in the treated and discontinued groups, respectively.

Survey participants were presented with 14 ADLs and asked current ability to perform each activity. Changes experienced over the previous 12 months - including improvement, decline, or no change - was assessed for all activities that the participant indicated they currently or previously had the ability to perform.
No individuals in the discontinued and untreated groups reported any ADL improvements. In the treated group, at least 1 individual reported improvement in 10 of the presented ADLs. The ADL reported to have highest proportion of individuals with an improvement was 'ability to hold a cup to drink' (8.5%). The ADL most commonly reported to experience decline was 'lifting arms overhead' for 61.5%, 71.4% and 50.0% in the treated, discontinued and untreated groups, respectively. Additional details on specific changes in ADLs will be reported.

This analysis provides real-world insight into changes in various ADLs over time among adults living with SMA, and may help guide more appropriate outcome assessments in this population.

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SMA 1 fast code: A strategy for the early diagnosis of Spinal Muscle Atrophy Type I as a neurogenetic emergency

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Spinal muscular atrophy (SMA) is a neuromuscular disease caused by alteration in the survival protein of motor neurons causing high morbidity and mortality, especially in patients with SMA type 1 so it is considered a neurogenetic emergency. Although many countries have implemented neonatal screening for SMA, however, there are countries in the world that do not have it, so the diagnosis and treatment of these children is often delayed.

Create a warning system based on signs and symptoms that allows not only early diagnosis of suspected SMA type 1, but also rapid action upon confirmation of the diagnosis.
Methodology: A systematic review of PubMed and Google Scholar was performed from inception to August 1, 2024 using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations, looking for the most frequent signs and symptoms in SMA I. Cohort studies, natural history, series and case reports were included.

A total of 145 studies were initially identified and 21 met the inclusion criteria by describing patients with SMA type 1 with baseline data, without therapeutic intervention or with information clearly differentiated from the pretreatment period. These included studies analyzed 537 patients with a diagnosis of SMA type 1. The remaining 127 studies were excluded. Based on the results, we calculated the frequency of signs and symptoms found and created the acronym SMA 1 FAST, which will give the name to the SMA 1 FAST Code. S: Respiratory distress 93.13%, M: Muscle weakness 93.41%, A: Areflexia 92.93%, 1 ≥ 1 relatives with suspected or confirmed SMA 32.00%, FA: Fasciculations in the tongue 86.62%, S: Suction and swallowing disturbance 65.67%, T: Tone (hypotonia) 97.44%. Scoliosis and bulbar palsy were excluded from the analysis

Codes have been created in neurological diseases that require rapid intervention and SMA, especially SMA type 1, having a rapid morbimortality, benefits from all possible strategies that allow early detection. Our study proposes the creation of the SMA 1-FAST code, which will not only alert the clinician to the suspicion of SMA type 1, but will also allow early diagnosis and treatment.

P193

Launching the rirst SMA patient registry in Vietnam: Patient-reported data, early insights, and patient participation

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Spinal muscular atrophy (SMA) is a severe neuromuscular disorder that causes progressive weakness and respiratory complications, leading to significant morbidity and mortality. In Vietnam, little epidemiological data exist, making it difficult for policymakers, clinicians, and advocates to assess disease burden or plan services. A national patient registry is crucial to quantify unmet needs, guide policy advocacy, and prepare for future therapy access. Registries also empower patients and caregivers by providing a structured platform to contribute experiences. Until now, no SMA registry existed in Vietnam, and no disease-specific therapies are available, underscoring the importance of this initiative.

In April 2025, we launched the first Vietnamese SMA patient registry, aligned with the Treat-NMD framework. Data are collected through patient self-reported questionnaires covering demographics, diagnosis, clinical features, treatment status, quality-of-life indicators, and affordability. Each patient is identified via a personal code linked to the Rare Diseases Registry of the Vietnamese Organization, ensuring confidentiality and standardized tracking. To promote engagement, patients and caregivers can view aggregated results, enhancing transparency and participation.

As of 28 September 2025, 194 patients from 30 provinces have been enrolled, demonstrating broad representation. Preliminary analysis shows 61.1% with SMA type 2, 19.7% with type 1, and the remainder type 3 or unclassified. More than half (56%) are under 6 years old—an important group as Vietnam's Social Insurance covers all treatment costs for children under 6 if a medicine receives approval. Although no SMA therapy is officially available, 26.3% of patients have received or are using at least one medicine, with two-thirds on oral drugs. Early affordability insights indicate only 6.7% of families reported capacity to cover at least 5% of the estimated gene therapy cost, highlighting substantial financial barriers. These data provide a first step toward shaping support policies through government, insurance, community fundraising, and treatment strategies. The registry also offers industry and policymakers a clearer view of patient needs, supporting future therapy introduction. Patient feedback shows that contributing and tracking results fosters engagement, ownership, and community solidarity.

The Vietnamese SMA registry demonstrates the feasibility of patient-reported data collection and transparent reporting in a resource-limited setting. Early findings highlight limited treatment access and severe affordability challenges, while providing an evidence base for advocacy, financial support, and future access strategies. Beyond data collection, the registry empowers patients, informs policy, and represents a landmark step for rare disease care in Vietnam, with potential as a model for similar initiatives in the region.

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Study of understanding patterns of exercises, physical activity and falls: What can we learn from a large real-world cohort of adult SMA patients?

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Spinal Muscular Atrophy (SMA) is a progressive neuromuscular disorder that significantly impairs motor function and limits physical activity. SMA patient attend more frequently to our neuromuscular/SMA clinics to access disease modifying therapies via Manage access agreement (MAA). In addition to motor and patient recorded outcome measures (PROM) assessments by physiotherapists, exercise, falls and injury risks and physical health related issues are reviewed in these clinics.

This is important especially due to maintaining appropriate levels of physical activity is essential for preserving functional ability and quality of life. However, standardized assessments of activity levels in the SMA population are limited. The Rapid Assessment of Physical Activity (RAPA) scale offers a brief, validated tool for evaluating physical activity in adults, yet its application in SMA has not been extensively explored. RAPA data is routinely collected in the SMA clinics.

Additionally, the falls are a significant concern for SMA ambulant patients. Due to muscle weakness, poor posture, increased fatigue and impaired balance patient with SMA are at increased risk of losing stability during transfers, walking and standing. Falls in SMA patients have not yet been explored using real world data.

The adult UK SMAREACH database hosts the data for over 350 SMA patients collected in "in-clinic assessments" which can be helpful in assessing exercise, falls and therapy levels of adults with SMA. The SMA Reach database currently collects data using the rapid assessment of physical activity scale, (RAPA1 and RAPA 2). We can use this data and compare it to the NHS recommended physical activity guidelines for adults.

Preliminary findings of this data this will help counsel SMA patients and SMA care teams about current physical activity levels at various functional stages of SMA in adults. This can in turn be used to compare with national recommendations and estimate if a patient in clinic is an outlier. Using the UK SMA reach database we can review how many SMA ambulant patients are experiencing falls and have a better understanding on how this may impacts their life.

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Severe Spinal Muscular Atrophy with concurrent SMN1 and NAIP Deletion: A case report

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Spinal Muscular Atrophy (SMA) is a rare autosomal recessive disorder, with an incidence of approximately 1 in 10,000 live births. It is primarily caused by a homozygous deletion of exon 7 in the survival motor neuron 1 (SMN1) gene located on chromosome 5q13.2. This results in progressive motor neuron degeneration, leading to global hypotonia, muscle weakness, and areflexia. Phenotypic severity, classified into five types, is inversely correlated with copy number of the homologous SMN2 gene and is further modified by the co-deletion of the neuronal apoptosis inhibitory protein (NAIP) gene. The presence of a homozygous NAIP deletion is a recognised biomarker for a more severe and progressive disease course, typically SMA Type 1. Early genetic confirmation is therefore critical for initiating timely therapeutic interventions and informing prognostic discussions.

An 8-month-old female infant was admitted to the hospital with a primary complaint of acute respiratory distress. Eleven days prior, she developed a fever, with cough and dyspnea. Upon presentation, she was febrile, tachypneic (RR: 45/min), cyanotic, and required immediate supplemental oxygen via non-rebreather mask. Physical examination revealed bilateral subcostal and intercostal retractions, with generalised hypotonia. The patient was alert and responsive. A chest X-ray confirmed bilateral pneumonia. The constellation of severe respiratory distress with global hypotonia raised strong clinical suspicion for SMA.

Genetic confirmation was obtained via PCR-Restriction Fragment Length Polymorphism (PCR-RFLP) analysis. Genomic DNA was successfully isolated from dried blood spots on an FTA Elute Microcard, yielding a high-quality concentration exceeding 100 ng/µL. Target regions of SMN1, SMN2 (exons 7 and 8), and NAIP (exon 5) were amplified and subsequently digested with the restriction enzymes DraI and DdeI to detect the presence or absence of specific homozygous deletions.
Results: Electrophoretic analysis confirmed a homozygous deletion of both exon 7 and exon 8 of the SMN1 gene. Analysis of the SMN2 gene confirmed the presence of both exons. Critically, a homozygous deletion of exon 5 of the NAIP gene was also identified. This genetic profile, homozygous SMN1 deletion coupled with a homozygous NAIP deletion, is a hallmark of the most severe phenotypic manifestation of SMA.

This case underscores the critical importance of prompt genetic testing for early SMA diagnosis, particularly in infants presenting with respiratory infection and profound hypotonia. The identified co-deletion of SMN1 and NAIP genes provides a molecular explanation for the severe clinical presentation and informs prognostic expectations. This finding highlights the utility of comprehensive genetic screening, including NAIP analysis, to guide clinical management and therapeutic strategies.

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Benchmark analysis of rehabilitation gaps in Spinal Muscular Atrophy: Insights from Slovenia, Bulgaria, and Turkey

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Spinal Muscular Atrophy (SMA) is a rare genetic neuromuscular disorder which is characterised by progressive muscle weakness and severe physical limitations. Beyond the clinical symptoms, SMA has a profound impact on patients and their caregivers. The need for continuous and intensive care often results in physical fatigue, psychological distress, social isolation, and financial strain, thereby affecting overall family dynamics and social inclusion.

Rehabilitation centres for neuromuscular diseases, including SMA, play a crucial role in improving the quality of life of both patients and their families. While existing literature has examined various aspects of SMA, cross-country comparative studies on rehabilitation experiences remain limited.

This study examines the SMA landscape and rehabilitation experiences in Slovenia, Bulgaria, and Turkey, offering a cross-cultural perspective on current practices, challenges, and potential actions for improvement.

P201

Impressions and impact of a children's literature project on health literacy and awareness of a rare condition through stories of a character with SMA

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In children's literature, there are still few books telling the stories of people with disabilities. By sharing information about diversity, a new knowledge about a certain diagnosis emerges, as well as an affectionate and humanizing view of people with disabilities. The "Aventuras de Titi" project refers to a series of publications of children's literature books and storytelling activities, meetings and talks based on the books. The stories are based on observations of the character's universe, inspired by a girl born with type 2 Spinal Muscular Atrophy. Titi has important questions, such as understanding her limitations, as well as giving light to reflections through the dialogues presented, and yet showing situations and curiosities common to any child her age. The project began in 2021 and remains active, with 8 titles already released, in Portuguese and English. More than 20,000 books have been printed and more than 12,000 books distributed free of charge, reaching more than 1,170 cities in all states of Brazil, with more than 10,000 opinion forms collected. Take-home messages: "The Adventures of Titi" widely distributes educational materials with representativeness, stories about different childhoods that are recognized by subscribers as important. Titi also encourages quality reading and knowledge, passed on in a light, playful and awareness-raising way, bringing inclusion through a character with a disability who is equally curious, adventurous and playful: a child. And it reinforces the need for children's literature that represents diverse characters.

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Spinal Muscular Atrophy patient journey in Minas Gerais: Mapping, challenges and perspectives

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Imagine the impact of bringing together 26 experts from different fields and reference services to develop innovative and collaborative solutions to the challenges of Spinal Muscular Atrophy (SMA). This was the proposal of the SMA Patient Journey in Minas Gerais project. SMA is a rare, genetic neuromuscular disease that compromises motor neurons, affecting essential functions such as walking, swallowing and breathing. The project aimed to map the patient's journey from the first symptoms to treatment, identify challenges, propose collaborative solutions, generate data and strengthen the health ecosystem in SMA care. For this, 123 interviews were carried out with patients, family members and health professionals, followed by collective meetings to prioritize challenges, co-create solutions, organize work groups and prepare materials for the improvement of SMA care. The mapping revealed recurrent difficulties in a rare disease trajectory: late diagnosis, lack of standardized protocols, bureaucracy in access to medicines and centralization of services. In the SMA Patient Journey, more than 50 opportunities for improvement were identified and two were prioritized: the need for standardized protocols in diagnosis and post-diagnosis; the need for decentralization of care. Medical and support therapy professionals participated in the project voluntarily, including teams from the three reference hospitals in SMA in Minas Gerais, in addition to six other institutions of great relevance in the state. The main deliverables of the project are: definition of care levels for patients with SMA; proposals for decentralization of care and scope of training of the care team; mapping of challenges in the patient's journey and the Emergency Card for patients with SMA. This project developed solutions, in line with the Continuing State Policy of Integral Care for People with Rare Diseases of Minas Gerais, which were validated by the State Department of Health and have great potential to contribute to the improvement of care. This is an example of how approaches structured in health innovation ecosystems and based on collaboration can generate effective results. Given the similarity of the challenges faced in other states, the project presents itself as a replicable model, with the potential to benefit patients with SMA across the country.

P205
Impact of SMA on oral health profile in children

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Spinal muscular atrophy (SMA) is the second most common autosomal recessive lethal disease, affecting newborns at a rate of 1 in 7,000. Recent studies have shown that SMA is associated with not only a lack of the Survival of Motor Neuron (SMN)-protein, which has a well-known impact of multi-organ functions, especially on muscle function, but also with a deficiency in collagen formation. Both, muscle function and collagen deficiency might have an impact on oral health due to dysfunctional chewing ability or malformation of oral structures. The present study aimed to assess the oral health profile of children with SMA and to compare it with healthy siblings, if present. Inclusion criteria were SMA (any type) in the patients' and no SMA in the siblings' group, and willingness to participate and informed consent from parents or legal guardians. Participants were examined by two experienced and calibrated dentists (LME and DK) using a mobile dental unit.

The following parameters were assessed: age, SMA type, number of SMN copies, current and previous medications, dental status (caries, fillings, missing teeth), proximal probing depth for all teeth, biofilm coverage (modified T-QHI), presence of calculus, incisal edge distance (IED), saliva pH and buffering capacity. The examination was performed under relative isolation; saliva samples were obtained after abstaining from drinking and eating for 30 min. Statistical analysis: Mann-Whitney and t-tests for comparison of groups, STATA 17, level of significance 0.05. Twenty-six SMA patients and 9 siblings were included (mean±SD age 9.8±3.8 y and 9.7±3.3 y, resp., n.s.). Most patients received a therapy with risdiplam (n=19), 4/2/1 with nusinersen/AVXS-101/BIIB115. Only minor differences in caries- (D) and filling- (F) values (mean±SD) were found (D-values: 0.19±0.98 patients and 0.11±0.33 siblings; F-values: 0.04±0.20 and 0.00±0.00, resp. (n.s.) with a concentration of caries on few patients. Similarly, only minor differences in mean probing depth were found (1.32±0.23 and 1.26±0.19, resp., n.s.). Biofilm coverage (T-QHI values) was higher in the SMA group on the oral (3.2±0.5 vs. 2.2±0.9, $p<0.001$), but not on the vestibular surfaces (3.1±0.9 vs. 2.5±1.1, n.s.). Ability to open the mouth (IED, mm) was lower in SMA patients (32.9±8.0 vs. 43.1±6.2; $p<0.001$). The same applies to saliva pH (6.8±0.5 vs. 7.2±0.3, $p<0.05$), but only in tendency for buffering capacity (6.3±3.6 vs. 7.2±2.7, n.s.). In summary, only minor differences in the presence of oral diseases (caries, filling and periodontitis) were found; however, the ability to open the mouth, the oral hygiene and the salivary parameters were impaired in SMA patients compared to the control group. This increases the risk of developing oral diseases over time, emphasizing the necessity of intensified preventive measures and regular dental check-ups to maintain oral health, chewing ability and quality of life.

P207

Nephrotic syndrome during long-term Nusinersen in 5q-SMA: Biomarker-guided differentiation from drug-related Nephrotoxicity

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A child with genetically confirmed 5q spinal muscular atrophy (compound heterozygote: maternally inherited SMN1 exon 7-8 deletion and paternally inherited SMN1-to-SMN2 gene conversion) has been treated with intrathecal nusinersen since 2019. During follow-up, he developed nephrotic syndrome with a steroid-dependent course requiring steroid-sparing immunosuppression (cyclosporine). Relapses were frequently temporally associated with systemic viral illnesses (including SARS-CoV-2 and influenza A/adenovirus) and were characterized by edema with nephrotic-range proteinuria (peak Esbach 8.5 g/day) and profound hypoalbuminemia (nadir 16 g/L), while kidney function remained preserved (serum creatinine ~24-30 umol/L). Given the regulatory requirement for renal surveillance during nusinersen therapy, we implemented a structured, dose-proximal safety pathway (urinalysis with protein quantification, serum albumin/creatinine, blood pressure, and cyclosporine exposure monitoring where applicable) to support decision-making on the timing of intrathecal dosing during nephrotic activity and intercurrent infection episodes. Across repeated nusinersen administrations over multiple years, creatinine remained stable and proteinuria fluctuations tracked nephrotic activity and infectious relapses rather than nusinersen exposure; during remission, urinary protein was low/negative at scheduled dosing visits. Nusinersen was maintained without interruptions attributable to renal toxicity, while nephrotic relapses were managed with standardized corticosteroid re-induction and immunosuppression adjustment under joint neurology-nephrology oversight. In the most recent follow-up, cyclosporine has been discontinued for approximately 12 months with sustained remission and no relapses while continuing nusinersen. This case suggests that nephrotic-range proteinuria arising in nusinersen-treated SMA may represent coincident glomerular disease rather than a therapy-limiting adverse effect, but mandates stringent pre-dose screening and close follow-up. A pragmatic co-management framework integrating infection-aware planning and proactive mitigation of nephrotic complications (fluid overload, thromboembolic risk, and procedure safety around lumbar puncture) can preserve uninterrupted access to disease-modifying therapy while maintaining renal safety.

P209

Instrumental swallowing assessment guiding clinical improvement in a child with Spinal Muscular Atrophy: A case report using videofluoroscopic evaluation

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Spinal Muscular Atrophy (SMA) is frequently associated with severe oropharyngeal dysphagia due to progressive neuromuscular weakness. Instrumental swallowing assessments play a critical role in identifying aspiration risk, determining feeding safety, and guiding clinical management in pediatric patients with SMA.

A two-year-old child diagnosed with SMA was referred for swallowing evaluation due to severe feeding difficulties. Initial clinical assessment revealed absent tongue movements, severely reduced oral motor control, and impaired swallowing function. Tongue lateralization and rotational movements were absent, and clicking sounds could not be elicited. Nutritional support was initially provided via a nasogastric tube and subsequently transitioned to percutaneous endoscopic gastrostomy (PEG).

Baseline videofluoroscopic swallowing study (VFSS) demonstrated significant pharyngeal residue and bolus flow toward the airway, indicating a high risk of aspiration and compromised swallowing safety.

An intensive dysphagia therapy program was initiated in November 2024, consisting of 3–4 sessions per week and continued over an eight-month period. A baseline videofluoroscopic swallowing study (VFSS) was performed prior to therapy in November 2024, followed by a repeat VFSS evaluation in September 2025 to objectively assess therapy-related changes.

Progressive improvements in oral motor function and swallowing efficiency were observed throughout the intervention period. Follow-up VFSS demonstrated marked improvement in swallowing safety, with reduced pharyngeal residue and improved bolus clearance. The child successfully transitioned to partial oral intake and currently tolerates 5–10 cc of milk pudding orally, with an approximate daily oral water intake of 500 ml.

This case highlights the value of longitudinal instrumental swallowing assessment in guiding individualized dysphagia management in pediatric SMA. The objective comparison of pre- and post-therapy VFSS findings over an extended period represents a novel clinical contribution, supporting the relevance of this case as a Late Breaking News submission.

P211

Intravenous Onasemnogene Abeparvovec gene replacement therapy for Presymptomatic Spinal Muscular Atrophy: Long-term follow-up analysis

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In the phase 3 SPR1NT study, presymptomatic infants with spinal muscular atrophy (SMA; two and three survival motor neuron 2 [SMN2] copies) treated at age ≤6 weeks demonstrated age-appropriate motor milestones, including sitting and walking independently with preserved bulbar and respiratory function after single-dose intravenous (IV) onasemnogene abeparvovec, supporting the benefits of early gene replacement therapy. Long-term safety and durability of IV onasemnogene abeparvovec were analyzed for these presymptomatic patients with SMA who enrolled in the LT-002 extension study (NCT04042025).

Long-term safety was assessed by medical history/record review, adverse events (AEs) (including serious AEs [SAEs] and AEs of special interest [AESI]), physical examination, laboratory evaluations, and pulmonary/cardiac assessments. Efficacy was assessed by demonstration of developmental milestones and change from baseline in Hammersmith Functional Motor Scale – Expanded (HFMSE). Two- and three-copy patient data are reported.

As of June 30, 2025, 27 presymptomatic patients (SMN2 gene copy number: two, n=13; three, n=13; four, n=1) treated with IV onasemnogene abeparvovec were enrolled in LT-002, with a mean (range) follow-up for two- and three-copy patients of 6.18 (2.8–7.2) years and mean (range) age at data cutoff of 6.25 (2.8–7.3) years. All patients were alive without permanent ventilation at data cutoff. Six patients (23.1%) (two-copy, n=4; three-copy, n=2) had AEs, and three patients (11.5%) in the two-copy cohort had SAEs. AESI included hepatotoxicity (n=1; 3.8%) and new incidence of neurologic disorders (tremor, hypotonia, balance disorder; n=4; 15.4%), all not considered related to the study treatment. Eight patients (30.8%) received add-on therapy (two-copy, n=6; three-copy, n=2). Seven two-copy patients demonstrated all motor milestones, including the highest milestone of walking alone, in the parent study; the other six patients demonstrated the remaining motor milestones in LT-002. Patients also demonstrated mean change from baseline HFMSE improvements of 15.5 (range 4–27) points for two-copy patients and 13.5 (range 1–36) points for three-copy patients in LT-002. No patient required invasive ventilatory support; 96.2% did not require any ventilatory support (two-copy, n=12 [92.3%]; three-copy, n=13 [100%]). Most patients (96.2%) did not require feeding support (i.e., feeding tube) at data cutoff (two-copy, n=12 [92.3%]; three-copy, n=13 [100%]).

Presymptomatic administration of IV onasemnogene abeparvovec alters the natural course of SMA such that patients demonstrate improved motor function and independence from nutritional and ventilatory support with no new safety signals for up to 7.2 years post-dosing.

P213

Global shifts in Spinal Muscular Atrophy classification and diagnosis: The transformative impact of newborn screening and disease-modifying therapies on clinical practice and patient outcomes

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The historical classification of spinal muscular atrophy (SMA) by types I-IV, based on age of onset and maximum motor milestone expected to be achieved, has long guided prognosis and care. However, this classification was defined in 1991 before the availability of disease modifying therapies (DMTs). In the era of early diagnosis via newborn screening (NBS) and effective DMTs, this phenotype-based typology is no longer adequate for guiding prognosis and treatment of SMA. Early treatment following diagnosis via NBS and a focus on functional status (non-sitters, sitters, walkers) are emerging as more responsive, patient centered frameworks that better reflect treatment outcomes.

To conduct a targeted literature review of recent publications synthesizing evolving diagnostic criteria and global trends in SMA diagnosis, highlighting the influence of NBS, DMTs, and motor milestone achievement on clinical practice and patient outcomes.
Methods: We reviewed recent consensus statements and guidelines for the treatment of SMA and integrated findings from clinical trials, real-world evidence, and systematic and narrative reviews. Key themes included diagnostic timing, motor milestone achievement, and global NBS adoption. Results: Historically, SMA diagnosis relied on clinical assessment and genetic confirmation after symptom onset, often following irreversible motor neuron loss. Classification by SMA type was useful to determine prognosis, but not treatment. With NBS now standard in numerous countries around the world, current SMA guidelines emphasize presymptomatic identification via NBS and immediate initiation of DMT. According to recent clinical guidelines and narrative reviews, results of SMA DMT clinical trials support that the motor milestones achieved by patients precludes their classification into historical SMA types. Data from the recently published STEER clinical trial further supports deviating from classifying patients by type, with clinically meaningful changes in motor milestones achieved for patients with SMA treated with intrathecal onasemnogene abeparvovec.

As patient outcomes continue to exceed historical expectations, there is a clear need to establish a new classification for SMA that reflects the current SMA landscape. The implementation of NBS and DMT initiation continues to transform SMA phenotypes, thereby rendering traditional type-based classification inadequate for capturing the nuanced and dynamic trajectories of treated patients. Implementation of NBS and DMTs have redefined SMA from a fatal infantile disorder to a treatable condition with near-normal developmental potential when therapy is initiated early. Harmonizing global NBS implementation and ensuring equitable access to early treatment remain urgent priorities.

P215 - FLASH TALK

Prenatal intervention in an SMA mouse model ameliorates neurodevelopmental disorders associated with spinal muscular atrophy

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Recent real-world data have shown that SMN-associated neurodevelopmental disorders (SAND) affect a proportion of children with early-onset Spinal Muscular Atrophy (SMA). We aim to characterise SAND in the severe (Taiwanese) mouse model of SMA using a range of behavioural tests assessing social behaviour and cognitive functioning. We explored rescuing SAND in the Taiwanese mice using either SMN-splicing modifier RO7021707, an analogue of Risdiplam, which enhances production of SMN protein levels from SMN2 gene, or PMO25, an antisense oligonucleotide that induces SMN2 exon 7 inclusion, administered at P0. Our goal was to test the efficacy of prenatal versus postnatal treatment in rescuing SAND due to the developmental impact of SMN deficiency on brain development and function.

Our findings reveal that the severe SMAI mice treated at P0 with either PMO25 or RO7021707, as well as the untreated mild SMAIII mice exhibited severe abnormalities in behavioural assays compared to healthy controls. These included the resident-intruder (that measures offensive aggression, defensive behavior and social stress), the marble burying (that measures repetitive and anxiety-related behaviors) and the 3-chamber (that measures social behavior). Motor function assessed with the grip strength test was normal. Importantly, SMAI mice treated prenatally (E13.5) exhibited behaviours similar to their control mice, suggesting a full neurobehavioural rescue with prenatal treatment.

No significant differences in the anatomy of cerebellum (H&E staining) and the number of neurons (NeuN+ cells) were observed between the different groups at 12 weeks. Protein analysis using WES revealed that treated severe SMAI mice had significantly lower SMN protein levels in cerebellum compared to WT or mild SMAIII mice.

Our findings suggest that SMN deficiency can cause developmental defects in the brain. We show that postnatal restoration of SMN is sufficient to rescue the neuromuscular phenotype but it is not sufficient to fully restore the behavioural phenotypes, which are rescued with prenatal treatment. Collectively, our studies indicate that SMN deficiency during development in the severe SMA mouse model is associated with neurodevelopmental defects that require prenatal treatment to be fully rescued. Further studies will investigate the molecular and cellular correlates of these abnormal behavioural phenotypes.

WORKSHOPS

WS1 - Organised by argenx & Karen Chen

Assessing fatigability in Spinal Muscular Atrophy: Exploring the contribution of neuromuscular junction dysfunction

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Although 3 survival motor neuron (SMN)-targeting disease-modifying therapies (DMTs) have been approved for the treatment of spinal muscular atrophy (SMA), a significant unmet medical need persists. A substantial proportion of patients are treated with ≥2 of the approved DMTs, yet many do not achieve optimal responses to these treatments. This highlights the limitations of current treatment options for patients with SMA and emphasizes the need for additional treatment options that better address disease symptoms.

Fatigability, a key symptom that significantly impacts the quality of life of patients with SMA, is emerging as a target of interest for therapeutic intervention; however, despite advances in SMN-targeting therapies, the effect on fatigability remains unclear.

Nonclinical studies have demonstrated that neuromuscular junction (NMJ) abnormalities are among the earliest and most pronounced pathological features in murine models of SMA. Some of these NMJ defects persist despite treatment with SMN-upregulating therapies. Emerging evidence indicates that modulation of the agrin–LRP4–MuSK–DOK7 signaling axis may offer a promising therapeutic strategy to ameliorate NMJ dysfunction in SMA. In addition, clinical studies have shown that NMJ functional abnormalities contribute to SMA disease pathophysiology. NMJ transmission deficits, evidenced by decremental compound muscle action potential amplitudes, persist in individuals despite treatment with DMTs. Off-label use of agents such as salbutamol, amifampridine (3,4-DAP), and pyridostigmine further supports the therapeutic potential of targeting NMJ integrity in SMA.

This workshop aims to present the role of the NMJ and to explore assessment strategies for evaluating fatigability in ambulatory and nonambulatory patients with SMA. In addition, the workshop will discuss sensitive outcome measures, including digital sensor technologies and the development of new scales to capture the intensity and duration of activity. These measures may enhance the detection of subtle changes in fatigability not captured with other assessments and support reported shifts in perceived fatigability, which may be used to measure potential treatment effects in investigational trials.

Targeting NMJ dysfunction may serve as a complementary approach to SMN-enhancing therapies, offering the potential to alleviate residual symptoms such as fatigability and muscle weakness that persist despite treatment with DMTs, thus highlighting the need for multimodal therapeutic strategies.

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WS 2 - Organised by Novartis

Beyond boundaries: Elevating SMA care for the future

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This impactful and dynamic workshop is designed to explore innovative strategies and collaborative approaches to optimize care for individuals with Spinal Muscular Atrophy (SMA) Types 2 and 3. Through a moderated panel and interactive live polling session, participants will engage in meaningful dialogue, share experiences, and develop strategies to address the unmet needs in SMA care.

Workshop objectives:

- Identify and address care gaps: Explore the current gaps and challenges in SMA care, particularly for Types 2 and 3, and discuss innovative strategies to enhance patient management and support systems.
- Foster multidisciplinary collaboration: Encourage collaboration among healthcare professionals, patients, and caregivers to develop a holistic approach to SMA care that integrates medical, rehabilitative, and psychosocial support.
- Empower and advocate for change: Empower participants to advocate for improved SMA care standards by sharing insights and experiences and inspire healthcare policies and practices for better patient access and outcomes.

Acknowledgment
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WS 3 - Organised by Kathryn Swoboda and Renske Wadman

Old signals, new insights: Electrophysiology as a biomarker in SMA

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In this workshop we dive into the motor unit pool, exploring the utility of electrophysiological measures as predictive biomarkers of (future) motor function in infants, children and adults with SMA.

Electrophysiologic studies (nerve conduction studies and electromyography) are potential important biomarkers to assess (pre)clinical disease activity in the motor unit, including axons, motor neurons and neuromuscular junction function. At this moment their use is limited in research and clinical care in SMA, but with the introduction of different therapeutic strategies at different disease stages it is even more important to find biomarkers that reflect disease activity and stage.

We will discuss the different opportunities and limitations of electrophysiologic studies and address the different techniques (standard nerve conduction studies, CMAP scan/MUNIX, repetitive nerve stimulation, electromyography) and proposed protocols (which nerves, what timing, in which patient). All techniques will be explained by means of clinical cases supported with data from the literature on SMA. In addition, we will discuss the opportunities for its use in future research and clinical setting.
At the end of the workshop, the audience will know what the different techniques withhold, how to use then (and when not to) and what the future perspectives of electrophysiology in SMA are.

WS 4 - Organised by José Longatto

MAPS - Mobility, Activity, Play, and Sports

J. Longatto

Great Ormond Street Hospital

The advances in drug and gene treatments for Spinal Muscular Atrophy (SMA) have significantly increased survival, improved physical function, and enhanced condition stability. The introduction of newborn screening has further reduced the impact of severe disability in many infants and children. Despite medical progress, physiotherapy remains a key part of long-term management for many with SMA. For those who can afford it—or where health or insurance schemes allow—infants, children, and young people may access regular professional input, mobility aids, equipment, and orthotics.

Many parents and children engage in stretching, exercise, and splinting routines, though many cannot. Physiotherapy should not stop with the therapist: it must become part of daily life—not just a routine, but an integrated, natural element. Framing physiotherapy as "work" or "routine" can cause guilt, resistance, stress, and fatigue for both parents and children.

Our workshop is designed for therapists but is equally relevant to parents, teachers, and carers. It introduces a new approach to home physiotherapy: the MAPS System—Mobility, Activity, Play, and Sports. This model is family-friendly, reducing the burden of adding another routine to busy lives. It promotes movement through enjoyable activities that fit into family and school life.

To help families use MAPS, we follow four guiding principles:

- Motivation: Embedding mobility and activity into things children already enjoy—football, dancing, or play—makes participation fun and purposeful. Motivation turns exercise from a chore into a natural part of life.
- Achievability: By adapting physiotherapy into manageable tasks, MAPS ensures success for every child. Adaptive strategies let children participate at their level, building confidence without pressure.
- Participation: Physiotherapy isn't just for the child. MAPS involves siblings, peers, and classmates so the child with SMA isn't isolated. Framing activities as shared games makes therapy inclusive and social.
- Support: Children thrive with consistent encouragement from professionals, parents, carers, and extended family. MAPS works across school and care settings, reducing parent burden. Importantly, it does not require costly equipment.

MAPS is achievable, functional, and fun. It has proven effective with parents, children, and therapists in the UK, Portugal, Latvia, and Lithuania.

Through MAPS—Mobility, Activity, Play, and Sports—physiotherapy at home is reframed: not as a chore, but as a sustainable, enjoyable part of everyday life.

SMA Europe 2026
5th International Scientific Congress
on Spinal Muscular Atrophy

Roche

Perspectives on real-world evidence in SMA care: **from shade to light**

Roche-sponsored symposium
Friday 13 March 2026 | 13:00–13:45 (CET)
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Harnessing real-world evidence to advance management of SMA

Prof. Eugenio Mercuri (Speaker)
Professor of Paediatric Neurology,
Catholic University of the Sacred Heart,
Rome, Italy

Insights from real-world evidence in adult SMA: motor and non-motor outcomes

Dr. Marcus Erdler (Speaker)
Head of the Neuromuscular Special Outpatient Clinic/
Competence Center for Neuromuscular Diseases,
Neurological Department, Klinik Donaustadt,
Vienna, Austria

Panel discussion with audience Q&A

Dr. Ksenija Gorni (Moderator)
Senior Global Medical Director,
F. Hoffmann-La Roche,
Basel, Switzerland

Visit the Roche booth (**#4**) to learn more about our commitment to SMA and engage with our representatives

We look forward to connecting with colleagues and the wider community

M-XX-00023078 | Date of preparation: February 2026

WS 5 - Organised by Esther Veldhoen and Lisa Edel

Respiratory care in Spinal Muscular Atrophy

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Respiratory muscle weakness in SMA causes reduced cough strength with recurrent respiratory tract infections and respiratory failure. Despite introduction of disease modifying therapies, respiratory symptoms are still present in many patients. For this reason, it is increasingly important to optimize supportive care to postpone or avoid respiratory failure. Assessment of respiratory function with early detection of deterioration of respiratory muscle strength is important to guide treatment.

The learning objectives of this workshop are:

- Physiology of respiratory symptoms in SMA
- Overview and (dis)advantages of different assessment tools of respiratory function used in clinical and research setting, such as lung function, tests of respiratory muscle strength, imaging studies, clinical scores.
- Evidence and use of different supportive respiratory treatments, such as airway clearance techniques and respiratory muscle training.

This will involve theoretical background, followed by practical hands-on sessions on respiratory muscle training and airway clearance, and an interactive discussion on clinical assessment tools to perform follow up on respiratory muscle weakness.
This workshop is primarily intended for clinicians (neurologists, physiotherapists, nurses, rehabilitation specialists etc). We specifically would like to invite patients to attend, as their expertise and input is useful for clinicians.

WS 6 - Organised by Simona Bertoli

Nutritional management in SMA in the new treatment era: From fundamental science to clinical practice

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The introduction of innovative therapies is profoundly changing the clinical phenotype of SMA, making accurate nutritional management a cornerstone for optimizing outcomes. Traditional tools like BMI are misleading in this population due to profound alterations in body composition (increased fat mass, reduced fat-free mass). Our multicenter research in Italy and the UK has addressed this by creating and validating a comprehensive assessment protocol with SMA-specific tools, including a standardized anthropometric manual, predictive equations for Resting Energy Expenditure (REE) and Fat Mass (FM%), and the first disease-specific growth charts. This interactive workshop aims to translate these research findings into daily clinical practice.

Objectives:

1. Present the rationale for a standardized nutritional assessment in SMA.
2. Train attendees on an anthropometric protocol adapted for neuromuscular disabilities.
3. Introduce new SMA-specific tools (predictive equations, growth charts) for accurate monitoring.
4. Discuss the interpretation of body composition data and its correlation with motor function.
5. Facilitate an interactive discussion on implementing these protocols in diverse clinical settings.

- The New Clinical Challenges (10 mins): In this opening session, Prof. Simona Bertoli will discuss how new therapies reshape SMA nutritional profiles, highlighting the limitations of traditional metrics and introducing the concept of "quality of weight", emphasizing a standardized, disease-specific assessment.
- Metabolic Dysregulation in SMA Models (15 mins): This session will provide the crucial pre-clinical context for the clinical findings. Prof. Melissa Bowerman will provide the preclinical context from animal models on altered energy metabolism, brown fat activation, and the potential of targeted dietary interventions.
- Impact of New Therapies in the Clinic (15 mins): Prof. Anette Hjartåker will present real-world data on how treatments affect nutritional status and dietary needs in SMA types II & III, reinforcing the need for careful and tailored nutritional support.
- Practical Demonstration (25 mins): Drs. Ramona De Amicis, Silvia Gallosti, and Melis Sevim will lead a demonstration of key anthropometric measurements, explaining how to overcome difficulties like joint contractures and how to use the online calculators.
- Bulbar Dysfunction & Nutrition (10 mins): Prof. Giovanni Baranello will link neurological progression to nutritional deficits, focusing on how bulbar muscle weakness (dysphagia) is a primary driver of malnutrition.
- Round Table Discussion (15 mins): All speakers will moderate an interactive Q&A on practical implementation challenges and fostering a collaborative network for standardized nutritional care.

WS 7 - Organised by Biogen and Eduardo Tizzano

Every motor neuron matters – Biomarkers and treatment choice in SMA

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With three approved therapies, and additional treatment modalities on the horizon, SMA patients and caregivers are benefiting from increased treatment choice. However, whilst each therapy is supported by a strong evidence package, what these data mean for setting and monitoring individual treatment expectations and responses, is less clear.

- What is my capacity for improvement?
- How do I know if my treatment response is optimal?

Biomarkers such as neurofilaments, electrophysiology measures, and muscle imaging provide real-time information on the disease evolution and response to treatments at the motor unit level, offering novel perspectives on these questions.
We invite PAGs, clinicians and basic researchers with an interest in patient empowerment to join this workshop. Together we will explore how introducing a common "language" to describe the health of an individual's motor units, may support informed shared treatment decisions and better follow-up.

Acknowledgment
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WS 8 - Organised by FundAME

Contractures in SMA: From scientific insights to therapeutic targets

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Contractures are a common and disabling musculoskeletal complication in SMA, reducing functional capacity, causing pain, and significantly impacting the quality of life of individuals living with the disease. Although disease-modifying therapies (DMTs) have transformed the course of SMA, contracture management remains a largely unmet clinical need and continues to rely on pre-DMT standards of care. Consequently, the management of contractures and muscle imbalance—unlike muscle function—has changed little with the advent of DMTs and still follows pre-DMT care practices. Despite the changes in the disease landscape, long term outcomes are often unsatisfactory for those with chronic SMA frequently persisting or worsening over time, highlighting the urgent need for novel therapeutic approaches. A central question—and the driving theme of this workshop—is whether contractures in SMA are solely secondary to muscle weakness, imbalance, and immobility, or whether additional SMA-specific mechanisms contribute. For instance, could SMN deficiency directly alter muscle or connective tissue properties, predisposing patients to contractures in ways distinct from other neuromuscular disorders? Preclinical evidence suggests that SMN deficiency induces intrinsic muscle abnormalities (non-neuropathic myopathy). Addressing these questions is essential for the development of novel, muscle- or tendon-targeted strategies that complement existing therapies and alleviate the burden of contractures. FundAME, SMA Europe and SMA Foundation recognize the urgent need to prioritize the understanding and management of contractures within the SMA research agenda. This workshop aims to promote a rigorous, multidisciplinary dialogue among researchers, clinicians, and patients.

Objective:

- To integrate current knowledge in basic research on muscle involvement in SMA, strategies used for its clinical management and identified patients' unmet needs, as well as therapeutic options.
- To identify new areas of research needed to improve the approach and treatment of contractures and, ultimately, the development of new approaches and specific drugs.

Acknowledgment

This workshop is offered by Roche.

WS 9 - Organised by Scholar Rock

Addressing unmet needs in SMA care through multidisciplinary collaboration and education

L. De Waele[1], M. Van Den Hauwe[2], L. Murto[3]

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Despite transformative progress, the SMA journey is not complete. Spinal muscular atrophy (SMA) has entered a new era, with survival motor neuron (SMN)–targeted treatments transforming outcomes and underscoring the importance of multidisciplinary care. Yet despite these advances, individuals with SMA and their caregivers continue to face persistent unmet needs related to muscle weakness. This ongoing weakness leads to deterioration in motor function and can negatively impact daily life and independence over time. As new therapeutic approaches emerge on the horizon, healthcare professionals (HCPs) and patient advocacy groups (PAGs) increasingly recognize critical gaps in medical education and the resources needed to support informed, collaborative decision-making in SMA care.

This interactive workshop will bring together HCPs and PAGs from the SMA community to discuss these challenges. The key topics will include: (1) the evolving unmet needs in the current and future SMA landscape; (2) the role of multidisciplinary care in optimizing SMA care; and (3) the opportunities to enhance medical education and resource development for HCPs and PAGs to support and advance SMA care.

Through case discussions, audience participation, and cross-stakeholder dialogue, the workshop will empower participants will co-create actionable insights to shape future educational priorities and strengthen support for individuals living with SMA.
This workshop is organized and sponsored by Scholar Rock, Inc. by way of financial contribution and provision of educational materials.

Acknowledgment
Supported by Scholar Rock.

WS 10 - Organised by Chiara Mastella

The role of early parental empowerment in management of emergencies and urgencies at home in pharmacologically treated SMA type 1

C. Mastella, M. Foà, M. Negri, E. Pagliaccia, M. Rauso, M. Antonella Costantino

Sapre- UONPIA Fondazione IRCCS Ca Granda Ospedale Maggiore Policlinico

Spinal Muscular Atrophy Type1 (SMA1), a severe neuromuscular disorder, has historically presented significant challenges, with respiratory complications being the leading cause of morbidity and hospitalizations, particularly in the context of managing home-based emergencies. Prior to the advent of disease-modifying therapies (Nusinersen, Onasemnogene Abeparvovec and Risdiplam), care was predominantly palliative. While these new treatments have profoundly improved clinical outcomes and prognosis, the complexity of home care for SMA1 remains, and the risk of respiratory crises persists. For this reason, respiratory physiotherapy protocols and the use of tools and devices that promote chest expansion, peripheral pulmonary ventilation, and airway clearance techniques, remain fundamental in daily care.

In this workshop we would like to share our long-standing multidisciplinary experience aimed at training and empowering families, as well as all the healthcare workers who support families, on managing respiratory emergencies at home. Education and psychological support for caregivers are fundamental parts of comprehensive disease management.

Our program begins at diagnosis and evolves alongside the patient's therapeutic journey. We identified six recurrent emergency scenarios: acute airway obstruction from secretions, respiratory decline during infections, ventilator malfunction, aspiration risk from vomiting, stress-induced respiratory distress and summer dehydration. All caregivers are required to complete a Pediatric Basic Life Support course.

Initially, our focus was on palliative care, teaching families to use basic resources like chest physiotherapy, suctioning, and Ambu bags to maintain a very basic quality of life. With pharmacological advancements, the emphasis has shifted to new needs and better quality of life.

Empowered families show increased competence, confidence, and proactive care in their child's care. Our results suggest that comprehensive, evolving training, and psychological support are integral to modern SMA1 management, leading to improved outcomes, reduced hospitalizations, and enhanced family well-being.

The advent of disease-modifying therapies has profoundly transformed the prognosis of SMA1, shifting the focus from predominantly palliative care to the long-term management of a chronic condition. Our multidisciplinary training program, which integrates psychological support with ongoing practical education, has demonstrated its effectiveness in reducing hospitalizations and boosting families' competence and confidence. As the clinical landscape continues to evolve, empowering caregivers and healthcare staff is crucial for optimizing long-term outcomes and fostering a proactive approach to care.

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Our ambition in Neuroscience is to create a meaningful impact for people living with severe neurological conditions and their caregivers by discovering, developing and delivering innovative medicines that change the course of disease progression.

FA-11588422-1 18/02/2026

WS 11 - Organised by Giovanni Baranello

SMA and neurodevelopmental disorders: A call for harmonized strategies

G. Baranello[1], S. Quijano-Roy[2], D. Gómez-Andrés[3], C. Brusa[1], Y. Erbas[4]

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The natural history of Spinal Muscular Atrophy (SMA) has significantly changed with the advent of SMN-enhancing therapies, leading to improved motor outcomes and prolonged survival, particularly in infants diagnosed through newborn screening. However, emerging evidence reveals that children with severe SMA—especially those with lower SMN2 copy numbers—may experience a range of neurodevelopmental disorders, including speech and language delays, autism spectrum disorder, global developmental delay, and intellectual disability. These findings challenge the traditional view of SMA as a purely motor neuron disease and underscore the need to understand its broader impact on brain development and overall quality of life.

Despite early therapeutic intervention, the long-term neurodevelopmental trajectories of these children remain uncertain. This workshop aims to address this critical gap by fostering a multidisciplinary dialogue among clinicians, researchers, patient advocates, and other stakeholders.

Key objectives include:

- Exploring the neurobiological basis of how insufficient SMN protein levels in the developing brain may contribute to neurodevelopmental impairments in children with severe SMA.
- Identifying early markers and risk factors to recognize children most vulnerable to neurodevelopmental disorders, enabling timely and targeted support.
- Discussing strategies for early intervention, family support, and developmental stimulation to mitigate the impact of these disorders and improve quality of life.
- Engaging the patient community and stakeholders to build a collaborative framework that supports families, informs healthcare systems, and promotes harmonized approaches to care and research.

Intended audience: clinicians, researchers, patients' representatives and all relevant stakeholders that are committed to improve SMA care. By bringing together diverse perspectives, this workshop seeks to catalyse a unified response to the emerging neurodevelopmental phenotype in SMA, ensuring that affected children receive comprehensive, anticipatory care that addresses not only motor but also the overall development.

WS 12 - Organised by Ewout Groen

Bench to bedside and back – Fundamental discoveries in connection with patient journeys

S. Bos[1], N. van Hoorn[1], M. Bowerman[2], L.M. Murray[3], W.L. van der Pol[4], R.I. Wadman[4], E.J.N. Groen[4]

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This interactive workshop explores the vital connections between patient experiences, and clinical and fundamental research through compelling case studies. Patient journeys, told by the patients themselves, will be supported by clinical and scientific insights from our research team.

The recent discoveries of effective treatments for patients with SMA are based on many years of fundamental research. However, SMA models differ in many ways from humans and often do not reflect the disease course of patients. For decades, researchers suspected limited correlation between phenotypic pathology and symptoms in severe animal models and patients. As we explore symptoms beyond motor neuron dysfunction, striking resemblances between severe animal models and patients are emerging. Depletion of SMN protein leads to structural and functional changes in kidney and pancreatic cells in severe animal models. Correspondingly, clinical changes in renal function and glucose metabolism are now recognized as significant features in adults with SMA. In addition, the discovery of structural NMJ changes in mouse models was followed by recognition of corresponding fatigability and functional changes of the NMJ in adults with SMA, leading to new treatment possibilities that improve NMJ function and reduce fatigability.

Adults with SMA represent the largest patient population and face unique challenges in managing systemic complications that can significantly impact their daily functioning and quality of life. During this interactive session, patients will share their lived experiences with altered glucose metabolism, renal function changes, and NMJ dysfunction. These personal narratives will be contextualized with insights into the fundamental scientific discoveries underlying renal function, glucose metabolism, and NMJ dysfunction research, and how these discoveries have influenced modern clinical care.

Personal stories from adults living with SMA will lead this workshop. By bringing together our varying backgrounds we aim to illustrate the importance of recognizing the full spectrum of SMA-related symptoms and the critical role that patient experiences play in advancing both our understanding of disease mechanisms and the development of practical solutions for managing everyday challenges and maintaining participation in society.

Objectives:

- Understand the bidirectional relationship between animal models and patient experiences in SMA research
- Recognize non-motor symptoms as integral components of SMA pathophysiology
- Appreciate how patient narratives can inform and validate preclinical research findings
- Explore emerging therapeutic approaches for systemic SMA complications.

Symposia

Sponsor Symposium organised by Novartis
12 March 2026: 13.00 - 13.45 hrs

SMA past, present and future

T. Hagenacker[1], J. Haberlova[2]

[1]University Medicine Essen, Dept. Of Neurology, Essen, Germany; [2]Universtiy Hospital Motol and Homolka, Prague, Czeck Republic

This medical symposium 'Redefining SMA: Past insights, present realities, future direction' brings together leading clinical voices, Prof. Jana Haberlová and Prof. Tim Hagenacker, and the lived experience of a patient advocate, Stefan Bos, for a dynamic, discussion-driven exploration of SMA.
Chaired by Prof. Jana Haberlová, this interactive session invites attendees to explore how our understanding of SMA has transformed, from its early clinical characterisation to today's rapidly evolving therapeutic landscape. The expert panel will discuss how the introduction of DMTs has reshaped the outlook for individuals with SMA, influencing clinical phenotypes and prompting new approaches to management, as well as shifting expectations among patients and their families.
Drawing on both clinician and patient perspectives, the faculty will highlight the historical context and current state of SMA care, while examining the key gaps and opportunities that remain in clinical practice. The discussion will also look ahead, considering how multidisciplinary pathways must adapt to optimise outcomes across an increasingly diverse and evolving patient population.
By blending scientific insight with real-life patient experience, this session aims to reshape how we think about SMA and inspire new approaches to management and patient involvement in decision making and overall care.

DMT, disease-modifying therapy; SMA, spinal muscular atrophy.
This medical education event is organized and funded by Novartis and is intended for an audience of healthcare professionals.

Sponsor Symposium organised by Scholar Rock
12 March: 17.30 - 18.15 hrs

Going beyond the motor neuron to the muscle: The case for targeting Myostatin in SMA

L. De Waele[1]; G. Peirens1, N. Deetens[2]

University Hospitals Leuven, KU Leuven, Belgium; [2]Caregiver

Join our panel of experts Prof. Liesbeth De Waele, Dr. Geertrui Peirens, and caregiver Nathalie Deetens for a 45-minute session: Going Beyond the Motor Neuron to the Muscle: The Case for Targeting Myostatin in Spinal Muscular Atrophy (Thursday 12 March, 17:30–18:15 CET, Patria Hall, Budapest Congress Center).

Despite transformative progress with SMN-targeted treatments, patients and caregivers emphasize that muscle weakness continues to impact daily life and challenge their ability to preserve independence. Experience with SMN-targeted treatments has also highlighted the value of early intervention and multidisciplinary care. This session will emphasize the critical role of muscle in SMA, explore the unmet needs related to ongoing weakness and motor function that remain, and review the scientific rationale for targeting myostatin. By integrating recent research, clinical insights, and lived experiences, this session aims to foster meaningful dialogue on the importance of specifically targeting muscle in SMA.

Sponsor Symposium organised by Biogen
13 March 2026: 08.00 - 08.45 hrs

Every motor neuron matters
Can neurofilaments be used to set and assess treatment goals in SMA?

S. Fradette[1]; M. García Romero[2], S. Kariyawasam[3]

PharmD, Head of Neuromuscular Development Unit, Biogen, Boston, MA, USA; [2]MD, Hospital Universitario La Paz, Madrid, Spain; [3]MBBS, PhD, Sydney Children's Hospital, Randwick, Australia

Neurofilament proteins have been validated as specific body fluid biomarkers of neuroaxonal injury. The advent of highly sensitive analytical platforms has enabled reliable quantification of neurofilaments in blood samples and simplified longitudinal follow-up. These advances are paving the way for the adoption of neurofilaments as a biomarker in clinical practice. Potential applications in spinal muscular atrophy (SMA) include assessment of disease activity, monitoring of treatment response, and determination of prognosis. Neurofilaments are also being used as an outcome measure in trials of disease-modifying therapies.1

In this symposium, we focus on the potential of neurofilament light chain (NfL) as a biomarker in both SMA clinical research and clinical practice.

1. Khalil M, et al. Nat Rev Neurol. 2024:20:269-87.
Biogen-275619. October 2025.

Sponsor Symposium organised by Roche
13 March 2026: 13.00 - 13.45 hrs

Perspectives on real-world evidence in SMA care: From shade to light

E. Mercuri[1]; M. Erdler[2], K. Gorni[3]

[1]Professor of Paediatric Neurology, Catholic University of the Sacred Heart, Rome, Italy; [2]Head of the Neuromuscular Special Outpatient Clinic/ Competence Center for Neuromuscular Diseases, Neurological Dept., Klinik Donaustadt, Vienna, Austria; Senior Global Medical Director, F. Hoffmann-La Roche, Basel, Switzerland

Roche is investigating more than a dozen medicines for neurological disorders, including spinal muscular atrophy, multiple sclerosis, neuromyelitis optica spectrum disorder, Alzheimer's disease, Huntington's disease, Parkinson's disease, Duchenne muscular dystrophy and autism spectrum disorder. Together with our partners, we are committed to pushing the boundaries of scientific understanding to solve some of the most difficult challenges in neuroscience today. Beyond our medicines, Roche is the leading provider of in vitro diagnostics, which are diagnostic tests conducted using samples such as blood or tissue from the human body. Diagnostics inform 70% of clinical decisions, including the prevention, identification and treatment of disease, and two-thirds of our R&D is focused on combining targeted therapies with companion diagnostics for better patient care. Roche's operating model of pharmaceuticals and diagnostics under one roof has enabled us to seek better ways to diagnose and treat some of the most challenging diseases of our time. We have already begun to uncover and pursue ways to bring promising new methods of diagnosis, progression monitoring and treatment access to the people and families living with nervous system disorders. Neuroscience is a cornerstone of our future. We will continue to push the boundaries of scientific understanding, together with our partners, to achieve clinical advancements and solve some of the greatest challenges in neuroscience today. Our hope is to create a tomorrow where nervous system disorders no longer limit human potential – to preserve what makes us who we are.

Advancing SMA care—together.

Progress starts with commitment. For over a decade, Scholar Rock's dedication to the SMA community has fueled our work to bring innovative solutions to life. We share your passion for serving those living with SMA, and we are here to support you in finding new ways to create possibilities.

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Biogen-Sponsored Educational Events

Every Motor Neuron Matters

Biogen-Sponsored Workshop

Biomarkers and Treatment Choice in SMA

In this workshop we will explore how a shared "motor neuron pool language" may empower patient participation in treatment decisions.

Intended for HCPs and researchers.

Wednesday 11 March 16:00–17:30
Room: Bartók II

Faculty:
Dr Eduardo Tizzano
Dr Sandi Kariyawasam
Dr Thomas Doktor
Dr Ankita Batla

Biogen-Sponsored Satellite Symposium

Can Neurofilaments Be Used to Set and Assess Treatment Goals in SMA?

In this symposium, we will discuss "use cases" to illustrate the potential role of neurofilaments as a biomarker in clinical practice.

Intended for HCPs and researchers.

Friday 13 March 08:00–08:45
Room: Patria Hall

Faculty:
Dr Stephanie Fradette
Dr Sandi Kariyawasam
Dr Mar García Romero

TIME IS MOTOR NEURON

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Biogen-278640. February 2026

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