Summary Report

Role of biomarkers in advancing access to treatments for individuals with neurocognitive or neuronopathic MPS conditions

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Renaissance Hotel, Schiphol Airport, Amsterdam

Hosted by:

MPS Society (UK) in association with International MPS Network

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CONTENTS

EXECUTIVE SUMMARY

This **multi-stakeholder meeting** brought together clinical and scientific experts, regulators, decision makers, commissioners, industry and patient organisations to **discuss the urgent need** for ethical, effective, and **efficient clinical trial** pathways in neuronopathic mucopolysaccharidoses (MPS). **Biomarkers** (BM) can play a **critical role** in assessing the efficacy of treatments, by providing objective measures of disease progression or response to therapy. The meeting focused on the role **of heparan sulfate (HS)** as a BM and **disease-driving metabolite,** and the importance of **integrating** BMs into **regulatory frameworks**.

DISEASE BACKGROUND

MPS are **ultra rare inherited lysosomal storage diseases (LSDs)** caused by **enzyme deficiencies** that prevent the normal breakdown of **glycosaminoglycans (GAGs)** including **HS** which leads to **progressive accumulation within the lysosome**, affecting **multiple systems,** including the **central nervous system (CNS).**

- Children with MPS typically appear **healthy at birth** and develop normally for the first **1–2 years** before experiencing a **decline**
- **Somatic symptoms** including recurrent infections, **developmental delays**, ENT issues, cardiac and skeletal abnormalities, hernias and abdominal distension, typically present in **early childhood**, though some **signs may present at birth** (e.g. hydrops fetalis, skeletal or facial abnormalities, hernias)
- In some MPS types (I, II, III, VII), children will also exhibit **neuronopathic features** including behavioural challenges (e.g. hyperactivity and aggression), cognitive regression and signs of dementia in late-stage disease
- MPS children have a **dramatically reduced life expectancy** and over time lose mobility and the ability to speak, eat, drink or breathe normally
- **Diagnosis is often delayed** due to subtle early signs and **multisystem symptoms,** leading to **multiple specialist referrals** and, in many cases, a **second affected child** being born before the first is diagnosed

CLINICAL TRIAL (CT) AND REGULATORY CHALLENGES IN NEURONOPATHIC MPS

Treatments such as **stem cell transplantation** and **enzyme replacement therapy (ERT)** exist for some MPS types. There are **no approved therapies for MPS III**, despite numerous global clinical trials involving hundreds of MPS patients, and no approved therapies exist to **cross the blood brain barrier (BBB)** and fully address **neurological symptoms**. CTs with promising results have **failed numerous times**, not due to a lack of safety or efficacy, but because **traditional CT models do not fit MPS diseases**. **Delays in approvals** are frustrating for parents who are watching their **children deteriorate** and **die.**

- **Challenges with capturing statistically significant meaningful outcomes on *cognitive endpoints*:**
  - **Long-term follow-up** is needed to show a measurable clinical benefit, resulting in **long CTs, delays to treatment access** and inability to sustain **long-term funding**
  - **Behavioural difficulties** in this population complicate cognitive assessments
  - Standard cognitive endpoints do not always reflect families' **real-world experience**

- **Disease stage impacts treatment response**, complicating interpretation of outcomes. As neurodegeneration cannot be reversed, in **post symptomatic** patients, **stabilisation is a meaningful outcome**, but it may take **years** to see a measurable departure from the typical disease course

- **Recruitment** for CTs in MPS is particularly challenging due to **diagnostic delays** and the **ultra-rare, heterogeneous** patient population, especially among **pre-symptomatic children** who stand to **benefit most from early intervention**
- **Placebo controlled trials** in MPS raise **ethical concerns** as patients in control groups are subjected to **irreversible neurodegeneration**
- CTs are often the sole opportunity for families to access treatment, however **participation is burdensome,** requiring **global relocation**, navigating **complex logistics,** and managing the **emotional strain** of caring for multiple children with MPS who may not all be eligible for treatment
- **Risk-benefit assessments** in MPS must account for the **certainty of disease progression without treatment**, which often outweighs the uncertain risks of intervention

SCIENTIFIC RATIONAL FOR HS AS A BM

- **HS is not just a biomarker but a toxic, disease-driving molecule**
  - It is **mechanistically linked** to the **underlying pathology** of neuronopathic MPS
  - **HS accumulation** causes **lysosomal dysfunction, neuroinflammation**, **mitochondrial damage**, and ultimately **neurodegeneration**
  - Progressive **neurodegeneration** occurs **only** in **MPS types** with **HS accumulation**
- The **pathological role of HS** has been understood for decades, studies across species (mouse, canine, human), with clinical evidence showing a **conserved link between HS accumulation and CNS damage**
- **CSF HS is CNS-specific**
  - **CSF HS levels correlate strongly with brain tissue HS** in animal models and human studies
  - Gene therapy studies in MPS IIIB mice demonstrated that **only CNS-directed therapies reduce both brain and CSF HS** confirming that CSF HS originates from the brain, making it a reliable and **specific indicator** of **CNS disease burden** and **therapeutic response**
- **CSF HS reflects dynamic changes in CNS activity**
  - CSF is **turned over rapidly** (~four times daily) allowing CSF HS levels to provide **early insight** into treatment response and neuronal activity
  - **CSF HS is more reflective of CNS pathology than serum enzyme levels,** which do not directly indicate therapeutic action within the lysosome
- **Validated and sensitive assays** now allow accurate measurement of HS in CSF and urine
- **Reductions in CSF HS correlate with improved clinical outcomes**
  - Multiple trials (e.g., UX111, RGX-121, tividenofusp alfa, OTL-201) have shown **dose dependent reductions in CSF HS** that correlate with **cognitive, behavioural** and

functional improvements, or **stabilisation** in advanced stage patients and **secondary markers** of neuronal injury and lysosomal dysfunction

- **Intrathecal ERT** in MPS IIIB canine models and Sanfilippo B patients, **reduced CSF and brain HS levels**, **prevented atrophy** and **improved behaviour** with a clear **dose-response relationship**
- These findings support **CSF HS** as **reasonably likely to predict clinical benefit** and a **valuable endpoint** for assessing **early therapeutic impact**

HS SUPPORTS MORE EFFICIENT AND ETHICAL CLINICAL TRIAL DESIGN

- **HS** enables **shorter trials,** providing **earlier insights into efficacy** than typical clinical outcomes, and reduces the need for **lengthy placebo arms** by dramatically **shortening the time** to demonstrate a positive **effect of treatment**
- **Delays in access** and **CT failures** have been due to **regulatory** and **funding barriers**. It is **untenable** for small biotech companies to sustain **decade long trials** to evidence benefit
  - HS enables more **efficient trial designs** by supporting the **interpretation of other endpoints, guiding dosing** and **signalling early immune response**
- **Earlier acceptance** of CSF HS could have **prevented trial failures**, **preserved promising programs**, and saved **critical time** for affected children

REGULATORY PERSPECTIVE

- The **U.S. Food and Drug Administration (FDA) supports** early use of **biomarkers** like CSF HS to **enable accelerated access in MPS**, with **long-term confirmatory data**
  - **CSF HS** has already supported **three Biologics License Application (BLA) submissions** as a **primary biomarker**
- The **Committee for Medicinal Products for Human Use (CHMP)/ European Medicines Agency (EMA)** maintain that **CSF HS is not yet sufficient for standalone approval**
  - **Clinically meaningful endpoints with placebo control remain essential** though emphasises the **importance of totality of evidence** over single statistically significant endpoints
- The **Medicines and Healthcare products Regulatory Agency (MHRA**) endorses **flexible regulatory pathways for rare diseases** and **may accept validated biomarkers as surrogate endpoints where strongly predictive of benefit**; less-validated biomarkers may also be considered under conditional approval or **Early Access to Medicines Scheme (EAMS)** if the benefit-risk profile is positive. New **MHRA guidance in 2025** will support the use of **historical and real-world data as external controls**
- Both **EMA** and **MHRA** are **open to discussion** and stress the importance of **assay validation** and **early engagement**, noting that **higher risk** may be acceptable **in high-need, ultra-rare conditions** like MPS

CALL TO ACTION: HS should be recognised as a **toxic, disease-causing metabolite** and accepted as a **valid surrogate endpoint** to **accelerate access to treatments** for neuronopathic MPS

PURPOSE OF THE MEETING

This meeting aimed to bring together clinical and scientific experts, regulatory bodies, decision makers, industry leaders, and patient organisations to foster **global information exchange**, stimulate discussion, and emphasise the **importance of incorporating biomarkers (BM) into regulatory frameworks for advancing treatment options in mucopolysaccharidosis (MPS) and similar diseases**. The meeting was an insightful event that provided the opportunity to think about these conditions with neurocognitive and neuropathic challenges. It also prompted discussion on how best to **conduct research ethically** to **generate the right evidence** to get the answers but at the same time to **satisfy regulators and payers**. The meeting did not aim for decision making outcomes, but rather to set the scene for a new way of looking at some of the evidence generation and demonstrate how **BMs such as heparan sulfate (HS) could provide a different way of measuring disease progression**.

PARTICIPANTS/ORGANISING COMMITTEE

PARTICIPANTS	ROLE	
Bob Stevens	Meeting host	Group CEO of MPS Society and Rare Disease Research Partners
Kim Angel	Meeting host	Executive Director, International MPS Network (IMPSN)
Sophie Thomas	Chief Programme Manager	Senior Head of Patient Services and Clinical Liaisons, MPS Society
CLINICAL AND SCIENTIFIC ADVISORS		
Professor Simon Jones	Consultant in Paediatric Inherited Metabolic Disease, Honorary MAHSC, Professor of paediatrics and translational medicine, Medical Director NIHR, Manchester children's clinical research facility & hospital	
Professor Maurizio Scarpa	Director of the Regional Coordinating Centre for Rare Diseases, Professor of Paediatrics at the Dept. for the Woman and Child Health, University of Padova, Italy, Co-Founder of the Brains For Brain Foundation, Coordinator of the European Reference Network for Hereditary Metabolic Diseases, MetabERN	
Dr Fiona Stewart MBE	Trustee & Chair of CSAC at MPS Society	
MEETING MODERATOR		
Sheela Upadhyaya	Life Sciences Consultant – Expertise in Rare Disease	

MEDICAL WRITING AND FACILITATOR SUPPORT		
Eva Raebel PhD	Senior Research & Medical Communications Manager	Rare Disease Research Partners
Marnie Ross	Senior Research Executive	Rare Disease Research Partners
Harriet Clayton	Coordinator, Clinical Trials	Rare Disease Research Partners

AGENDA

Time	Title	Speaker	Affiliation
9.00	Introduction to meeting / housekeeping / agenda	Sheela Upadhyaya	
9.05	Welcome	Bob Stevens	MPS Society / RDRP, UK
9.10	Introduction and scene setting	Maurizio Scarpa Simon Jones	University Hospital Udine, Italy University of Manchester, UK
Part 1- Clinical and patient perspective			
9.20	MPS disorders – an overview	Fiona Stewart	MPS Society, CSAC, UK
9.30	The uncertain path towards approval Post trial experience Community perspectives: Acting on opportunity	Mark Dant Kim Stephens Cara O'Neill	Ryan Foundation, USA Muenzer MPS Research & Treatment Center, USA Cure Sanfilippo Foundation, USA
10.00	Heparan sulfate as primary cause of the neurological derangement in MPS	Maurizio Scarpa	University Hospital Udine, Italy
10.10	Clinical trials need biomarkers	Simon Jones	University of Manchester, UK
10.20	Discussion	Moderator led	
10.30	**Break**		
Part 2-What does the science tell us? (rationale for heparan sulfate as a biomarker)			
10.50	Development of heparan sulfate assays	Frits Wijburg	Amsterdam UMC, Academic Medical Center
11.00	Determining the origin of CSF heparan sulfate using biological compartment specific gene therapy	Grant Austin	Washington University School of Medicine Department of Pediatrics USA
11.10	Comparative and preclinical medicine	Matthew Ellinwood	National MPS Society, USA
11.20	The role of heparan sulfate in advancing clinical trial development	David Whiteman	MPS Society, CSAC
11.30	Impact of trial failure on clinicians and patients	Spyros Batzios	Great Ormond Street Hospital, London, UK
11.40	Discussion	Moderator led	
11.55	**Lunch**		
Part 3- Currently accepted and evolving evidence			
13.00	Tividenofusp alfa (DNL310) Clinical Trial for MPS II	Carole Ho	Denali Therapeutics
13.15	The use of heparan sulfate as a surrogate biomarker in MPS II as part of investigational RGX-121 gene therapy program (CAMPSIITE® Phase I/II/III)	Nidal Boulos	Regenxbio
13.30	Treatment with UX111 gene therapy rapidly reduced heparan sulfate (HS) exposure in cerebrospinal fluid (CSF) and improved long-term cognitive function in children with mucopolysaccharidosis IIIA (MPS IIIA)	Heather Lau	Ultragenyx

13.45	Clinical evidence OTL-201 - HSC-GT approach, proof of concept in neurometabolic disorders and OTL-201 registrational study design	Leslie Meltzer	Orchard Therapeutics
14.00	Discussion	Moderator led	
14.20	**Break**		
Part 4 – Views from the regulators			
14.35	Overview and outcomes from the Reagan Udall Foundation public workshop Overview and outcomes from the Reagan Udall Foundation public workshop from an academic perspective	Susan Winckler Joseph Muenzer	Reagan-Udall Foundation for the FDA, USA University of North Carolina at Chapel Hill, USA
14.55	Facilitating accelerated approval	Peter Marks	Center for Biologics Evaluation and Research, FDA, USA
15.10	European Medicines Agency (EMA) /EU Network presentation	Emmely de Vries, Jan Span	EMA / EU Network representatives
15.25	Medicines & Healthcare products Regulatory Agency (MHRA)	Shirley Hopper	MHRA, UK
15.40	Discussion	Moderator led	
Part 5 – Summary and final thoughts			
16.00	Panel discussion (Cara O'Neill, Joseph Muenzer, Simon Jones, Matthew Ellinwood)	Moderator led	
16.20	Closing remarks	Kim Angel	
16.30	End	End	

INTRODUCTION

KEY MESSAGES:

- Early treatment transforms outcomes in MPS patients
- Traditional clinical trial models based on clinically meaningful endpoints like cognition are inadequate for MPS; risk/benefit must weigh treatment risks against the certainty of progressive neurodegeneration without intervention
- Collaboration and advocacy are crucial to advance treatments in MPS

Welcome

Bob Stevens (BS), MPS Society / RDRP, UK

A call to action: Families affected by MPS deserve timely access to treatment and the chance at a good life—delays are no longer acceptable

BS shared his experience over the past 25 years as a father of two sons with MPS II, highlighting the impact of delayed treatment due to lengthy clinical trials (CTs). He emphasised the challenges of living with constant uncertainty and limited time, describing the contrast between his youngest son who received treatment at age four and now lives an active life and his older son who did not receive treatment until age seven and faces significant health issues and limitations. He emphasised the value of resilience and the vital role of patients, families, and advocacy groups as equal partners in shaping care. He urged attendees not to wait for opportunity, but to create it. Collaboration is key to improving outcomes for families living with MPS – because everyone deserves a good life.

Introduction and scene setting

Maurizio Scarpa (MS), University Hospital Udine, Italy
Simon Jones (SJ), University of Manchester, UK

"We are now in a position to change the course of MPS; as physicians, **if we can do something, we must do something"**

MS opened by emphasising this meeting starts the efforts to shorten time to treatment and improve outcomes for MPS patients. While care was once limited to only diagnosis and monitoring, the last 20 years have seen major advances in therapeutic approaches, including small molecules, gene therapy, and enzyme replacement therapies (ERT), with clinical trials showing promising progress.

SJ stressed the urgency of rethinking trial design and approval pathways in MPS. Despite promising results, many trials have failed to gain approval due to endpoints that do not reflect meaningful benefit. He stressed that MPS does not fit the standard trial model, and a focus on traditional clinically meaningful endpoints like cognition has not yielded clear evidence. For MPS, the risk/benefit assessment must consider not just the intervention's risks, but also the certainty of disease progression and neurodegeneration without it.

MS emphasised that earlier treatment significantly improves outcomes in MPS. Advances in diagnostic technologies, including newborn screening, allow for early intervention targeting the root cause of the disease, while new therapies that can cross the BBB can address neurological symptoms.

PART 1 - CLINICAL AND PATIENT PERSPECTIVE

KEY MESSAGES: CLINICAL AND PATIENT PERSPECTIVE

Disease background and diagnosis

- MPS are ultra-rare, inherited lysosomal storage disorders (LSD) with progressive multisystem involvement and neuronopathic subtypes (e.g. MPS I, II, III, VII) causing severe cognitive decline and behavioural issues alongside somatic issues
- Diagnosis is often delayed, with most children already symptomatic or declining at diagnosis, missing the window for optimal treatment

Importance of early intervention

- Earlier treatment leads to significantly better outcomes, particularly for neurological symptoms
- Treating pre-symptomatic children offers the best chance to prevent irreversible decline, but this requires newborn screening, which is currently limited due to lack of approved therapies
- **Stabilisation is a meaningful outcome** in progressive irreversible diseases

Limitations of current CT models in MPS

- Standard CT designs fail in MPS due to:
    - Long disease progression timelines
    - Small, heterogeneous patient populations
    - Cognitive endpoints that take years to show change
    - Ethical issues with placebo use in neurodegenerative conditions
- Families face extreme burdens to access trials including relocating, caring for multiple affected children, and coping with exclusion due to advance disease stage
- Mobility, feeding, and communication are meaningful to families but often not captured in CT assessments
- Without reform, children and families continue to bear the cost of regulatory inaction

The use of HS as a BM

- HS is not just a BM but a toxic molecule that drives the disease pathology via neuroinflammation, mitochondrial dysfunction, and lysosomal impairment
- Reducing CSF HS correlates with clinical stabilisation and reflects brain pathology

There is an urgent need for better outcome measures to support more efficient and ethical CT design because children with MPS do not have time to wait

MPS disorders – an overview

Fiona Stewart, MPS Society, CSAC, UK

SUMMARY

- MPS are **rare inherited LSDs** caused by **deficient enzyme activity**, leading to **toxic accumulation of GAGs,** including **HS**, and resulting in **progressive multi-systemic** damage
    - **HS is not just a BM, but an active promoter of disease**
- **Diagnosis is often delayed** as symptoms present at birth are subtle, and later **multisystemic symptoms** mean children see **multiple specialists** and experience significant progression before reaching a diagnosis
- **Symptoms emerge in early childhood,** including recurrent infections, ENT issues, cardiac and skeletal abnormalities, and in MPS III, gastrointestinal symptoms. As the disease progresses, patients with neuropathic forms of MPS may exhibit autism-like features, behavioural issues, seizures, and cognitive decline
- **CT participation is difficult** for families who often have **more than one affected child** and **complex medical needs**. Many face significant **logistical and emotional burdens**, especially when children are deemed too progressed to participate
- **Treatment options remain limited.** While **stem cell transplant** and **ERT** exist for some MPS types, these **do not address neurological symptoms**, **and no approved treatments exist for MPS III**

MPS are inherited LSDs and are mostly autosomal recessive with one in four children of carrier parents affected. MPS II however is X-linked and primarily affects males. The lysosome acts as a 'recycling plant' to breakdown large molecules. In MPS, reduced or non-existent enzyme activity prevents this process, causing a build-up of glycosaminoglycans (GAGs) throughout the body, including HS. This build-up of toxic GAGs causes damage to cells leading to the clinical features of MPSs.

Early symptoms and diagnosis

MPS disorders are rarely diagnosed during pregnancy unless there is a previously affected child or severe complications, e.g. hydrops fetalis. Some signs may be present at birth, such as skeletal abnormalities (e.g. talipes, pectus, gibbus), hernias, corneal clouding, a swollen abdomen, or unusual facial features, but these are often subtle and rarely lead to early diagnosis. The multisystemic range of symptoms means a child with MPS may see many different consultants before the correct diagnosis is made.

- Delayed diagnosis often means a second child is born before the first is diagnosed with MPS, thus creating a huge burden of care

Symptoms in early childhood

Initially, development often appears to be normal, but then a range of issues emerge requiring significant multidisciplinary healthcare involvement including:

- Ear, nose and throat (ENT) issues, such as enlarged tonsils, enlarged adenoids, otitis media, hearing loss, nasal discharge, loud snoring
- Developmental delay
- Recurrent chest infections
- Cardiac problems
- Skeletal issues including hip dysplasia, genu valgum (knock knees)
- Hernias and enlarged abdomen due to hepato-splenomegaly
- In MPS III, GI symptoms are often mistaken for inflammatory bowel disease

Disease progression

Many individuals with MPS will have neuropathic involvement often presenting as features of autism or attention deficit hyperactivity disorder (ADHD). As the condition progresses children lose acquired skills, may experience seizures and develop behavioural problems such as hyperactivity, aggression, poor sleep and signs of dementia later in the illness. These behavioural symptoms can complicate CT participation. Over time, children lose mobility and the ability to eat and drink, often requiring tube feeding. Life expectancy is reduced, e.g. the mid-teens for MPS III individuals.

Current treatment options

Treatment options include hematopoietic stem cell transplants (HSCT) for MPS I and ERT for MPSI, II, IV, VI, VII to ease somatic symptoms, however it does not address neurological symptoms (e.g. in neuronopathic MPS II) as ERT cannot cross the BBB. No treatments are currently licensed for MPS III. While ongoing trials show promise, positive outcomes demonstrating clinical benefit remain challenging, so there is still a major unmet need in treatments for neuronopathic MPS.

Participation in CTs

Participation in CTs is extremely challenging for families due to complex medical needs. Given the rarity of MPS, there is need to travel long distances or relocate, which is especially difficult for families caring for an older child with advanced disease who is not eligible for the trial. **It can be devastating for families to learn their child is too advanced in the disease to qualify for a CT**.

The uncertain path towards approval

Mark Dant, Ryan Foundation, USA

SUMMARY

- **HS reduction strongly correlates with benefit,** yet traditional endpoints and randomised controls are still required
    - In a trial, all children showed **cognitive stabilisation and 70–80% HS reduction**, yet a **placebo-controlled** design was still **mandated,** leading to i**rreversible decline** in some patients
- **Stabilisation**, not just improvement, is **meaningful**; families often view disease progression as riskier than treatment

- **Regulatory systems must evolve urgently** to allow timely access and support **accelerated pathways** for ultra-rare diseases
- Mark's son, now 36, is living proof that **long-term treatment** can lead to a **full, independent life**

MD shared his experience as a father of an adult with MPS diagnosed over 30 years ago when no treatment existed and life expectancy was 10–15 years. MD's son was enrolled in a US CT aged 10, by which point the build-up of GAGs was already having a devastating effect. All ten patients on the trial improved, HS levels decreased by 70%–80%, correlating with stabilised cognitive scores (Bayley Scales). While initial reviews by the US Food and Drug Administration (FDA) suggested an accelerated data review could take place based on the decrease in storage of the disease-causing BM, ultimately a double-blind placebo-controlled trial was required leading to irreversible harm for some children, and despite evidence of treatment benefit. There are ethical concerns of requiring placebo arms in rare neurodegenerative diseases, something not permitted in paediatric cancer trials. He noted that CTs for approved ERTs since all were required to include a control arm despite all showing a reduction in the disease-causing BM and improved survival and quality of life for participants.

MD shared the story of a young girl with MPS IIIA who at 3 years old participated in a trial for an ERT with the potential to cross the BBB. After only a few weeks on treatment, her stutter disappeared, and study results showed that the drug passed the BBB in all patients. She remained stable for several months after the trial ended due to sponsor reprioritisation but then started to regress so that over 18 months, she lost most of her large vocabulary.

MD stressed that MPS can only improve with a reduction in HS and stabilisation is meaningful for families who often feel risk lies in the disease itself, not the treatment. His son, now 36 years old, is the longest treated person with MPS worldwide. Treatment has allowed him to graduate college, get married, work full time and to be alive for when even better science arrives. Yet, global regulators still have not accepted that reducing substrate accumulation improves quality of life and extends survival. Regulatory systems must evolve with the science to make continued treatment development financially viable for companies. Immediate action is needed from EMA partners to give this generation of children a future.

Post trial experience

Kim Stephens, Muenzer MPS Research & Treatment Center, USA

SUMMARY

- KS shared her son's discontinued trial experience where clinical benefit could not be evidenced due to **challenges in assessing cognitive endpoints**
- Highlighted the **emotional toll** and tragic consequences of **delayed access** and **placebo-controlled trials** in MPS
- Emphasised the **urgent need** for **better outcome measures** because **children with MPS do not have time to wait**

KS shared the story of her son, who has severe MPS II. After normal early development he lost the ability to speak by age 9. He took part in an intrathecal enzyme trial at age 4, which involved monthly sedation and lumbar punctures. Despite a low drug dose, his HS levels dropped. However, his refusal to engage with cognitive testing led to a score of zero and after 10 years, the trial was discontinued due to lack of measurable endpoints, despite clear signs of benefit. KS stressed that if HS had been accepted as a BM, the trial might have continued, and clinical benefit could have been evidenced at a later stage. Although no longer speaking, thanks to treatment, KS's son at 14 can walk, feed himself, breathe without assistance, goes to school, can run to the school bus and completes jigsaw puzzles while many other children have been waiting for a treatment. She called for better outcome measures because children with MPS do not have time to wait.

She highlighted the emotional toll of placebo-controlled trials, describing the anguish of waiting to learn if a child received treatment, and the heartbreak of a mother whose son was excluded and died waiting for approval that came too late. **No parent should have to watch their child die when a potential treatment exists.**

Community perspectives: acting on opportunity

Cara O'Neill, Cure Sanfilippo Foundation, USA

SUMMARY

- Many **promising therapies** have failed due to reliance on **cognitive endpoints** and the inability to use **BM-based approval**
- **Two-year** trials are too short to demonstrate **meaningful cognitive benefit** in MPS III; **longer timelines** are needed, especially for Types B–D. Small biotech **companies struggle to sustain long trials** and capture **statistical significance** leading to shelved programs or company closure, **ultimately delaying treatments**
- **Patient-centric outcomes** like feeding, sleep, and communication must be **prioritised over cognitive measures,** which are **slow to show change** and difficult to assess in this population
- **HS** is a strong BM **reasonably likely to predict benefit**; adopting it as a primary endpoint could enable **more ethical, timely trials**
- **Withholding treatment** through long **observational phases** or **placebo arms** in a **progressive, irreversible** disease is increasingly seen as **unethical**

CO'N the mother of a child with Sanfillipo (MPS III), highlighted the devastating toll on children and their families and the urgency of timely treatment. Beyond multisystemic symptoms, MPS III particularly affects the central nervous system. At birth, children appear normal, followed by typical early development, then a plateau, and eventually a decline with loss of previously acquired skills and behavioural issues. Symptoms often begin in early childhood, and without newborn screening diagnosis, is typically delayed until ages 4–6when irreversible neurological damage is already significant.

Despite a well-documented disease course and cognitive decline timeframes, no approved therapies exist for any form of MPS III or other CNS-directed neuronopathic MPS conditions.

Many trials have failed due to reliance on cognitive endpoints that require long timelines to demonstrate a deviation from the normal disease course in this population, well over the duration of typical CTs. Promising therapies have been shelved due to the inability to access approvals based on BMs or sustain long-term trials.

Without the ability to access BM-based approval, companies have repeatedly shelved their programmes/returned them to academia/gone out of business. CO'N stressed that while early treatment offers the best outcomes, most children are already symptomatic at diagnosis therefore measures that assess meaningful benefits are needed to address these patients' needs. Caregiver studies show that treatment priorities include reducing pain, enabling feeding, sleep, walking, and communication [Ackerman Porter K et al, 2022]. These outcomes are not typically prioritised in many trials but now being considered.

MPS involves a race against time; as the disease progresses so does neurodegeneration. Lengthy trials impact companies' ability to continue to engage in drug development and ultimately, children and families bear the full weight of delays, making timely action critical. We must confront the ethics of withholding potential treatments (either due to randomisation or a required lead-in observational phase) in these irreversible neurodegenerative diseases' CTs. CO'N presented the example of a child diagnosed with MPS IIIB at 2.5 years old who took part in a trial which required a one-year observational period before commencing active treatment. During this period, their condition rapidly deteriorated and lost key abilities (including following directions, speech, play) that they will never regain.

With a strong BM like HS that is reasonably likely to predict long-term benefit, there is the opportunity to develop more ethical studies. **Delaying treatment in irreversible neurodegenerative diseases is no longer acceptable.** It is time to adopt HS as a primary BM, implement fit-for-purpose outcomes, and design trials that meet urgent patient needs.

Heparan sulfate as primary cause of the neurological derangement in mucopolysaccharidosis

Maurizio Scarpa, MetabERN, University Hospital Udine, Italy

SUMMARY

- **HS is not just a BM but a toxic molecule that contributes directly to disease pathology and must be targeted in therapy:** HS toxicity is evidenced by its role in immune activation, neurodegeneration, amyloid-beta accumulation, and widespread cellular inflammation beyond the lysosome (e.g. mitochondria)
- **CNS-specific impact**: HS accumulation triggers a cascade from glial activation to neuron death, a **slow process** that allows a **window for early therapeutic intervention** to **prevent irreversible neurodegeneration**
- **Call to action: HS** should be treated as a **primary disease activity BM.** Early and sustained reduction can target the root cause of the disease to prevent irreversible damage and **improve outcomes**

In all neuronopathic MPS types, neurological symptoms progressively worsen, severely affecting quality of life. Clinical features include MRI abnormalities, cognitive decline,

behavioural and motor disturbances, sleep issues, seizures, and impaired swallowing and reflexes. These reflect progressive brain damage driven by HS accumulation in the CNS.

HS is not just a BM but a toxic molecule that contributes directly to disease pathology

HS accumulation has been shown to lead to inflammation, neurodegeneration, and mitochondrial dysfunction, protein misfolding, and impaired autophagy. Evidence of HS toxicity can be seen in the brain and in other systems:

- HS impairs donor cell engraftment in allo-HSCT via immune activation [Brennan, 2012]
- HS has been implicated in Alzheimer's and Down syndrome-related neurodegeneration [Snow AD et al, 1990]
- Accumulation of intracellular amyloid-beta peptide (A beta 1-40) found in MPS brains [Ginsberg DS, 1999]
- HS mediates internalization and cytotoxicity of amyloid-beta peptides [Sandwall E et al, 2010]
- HS is a mediator of inflammation [Ruijter J et al, 2012]
- Inflammation due to HS affects not just the lysosome, but also other cell compartments including the mitochondria [Martins C, 2015]

Proposed model of cell death in LSD

In the normal brain, cells such as microglia and astrocytes function by supporting neurones, but if there is a neuroinflammation, such as in MPS III, reactive microglia and reactive astrocytes contribute to inflammation in the brain and neurodegeneration.

In MPS III, a cascade of events is triggered by HS accumulation due to the enzyme deficiency: impaired autophagy, accumulation of toxic protein accumulation, mitochondrial disfunction and chronic inflammation leads to cell death. This slow progression from neuroinflammation to glial degeneration to neuronal degeneration starting in white matter and advancing to grey matter [Zalfa C et al, 2016], provides a window for therapeutic intervention before irreversible damage occurs.

Call to action: Fight HS

HS should be recognized not only as a BM, but as a **primary disease activity BM.** Actively correcting elevated HS is essential to:

- **Manage symptoms:** Reducing HS can alleviate many clinical manifestations associated with its accumulation and improve quality of life
- **Prevent irreversible damage:** Early reduction helps delay or avoid further CNS and systemic injury
- **Improved outcomes and survival:** Sustained correction can reduce the risk of complications (cardiac issues, respiratory problems and neurological decline) and extend patients lifespan
- **Targeting the root cause**: Correcting the biochemical imbalance itself addresses the fundamental cause rather than just the symptoms, aligning with precision medicine principles
- **Enables holistic assessment:** HS reduction, paired with clinical measures, provides a comprehensive view of therapeutic benefit

Clinical trials need biomarkers-lessons from MPSIII

Simon Jones, University of Manchester, UK

SUMMARY

Traditional trial designs and cognitive endpoints are not fit for neuronopathic MPS

- Most trials enrol **post-symptomatic children** where cognitive decline and behavioural issues complicate assessment; **benefit may take 5–10 years to demonstrate**, this is **unsustainable** for many sponsors
  - Stabilisation or slowed progression should be recognised as meaningful outcomes
- Pre-symptomatic trials face major challenges including **global recruitment, family relocation, and long timelines** to show a divergence from the normal disease trajectory. **Newborn screening** is not possible without approved therapies.
- **HS is the most proximal BM available**. Despite differences in early and late treatment effects, it enables **early insight** into therapeutic effect, guides dosing, **shortens trials** and supports more **ethical trial designs**
  - **Example:** A 2010 intrathecal ERT trial failed partly due to inaccurate early HS assays leading to underdosing; better BMs could have supported success
- **New CT approaches are essential.** Prolonged follow-up with placebo arms is unrealistic, **BM driven designs are key** to progress in neuronopathic MPS

Over the past 20 years, MPS CTs, particularly for neuronopathic forms, have used various designs and endpoints but with limited success. Natural history studies of MPS IIIA [Shapiro EG, 2016] show that untreated individuals experience normal early development, hence the diagnostic delay, followed by a period of plateau and then skill loss. While tools like the Vineland Adaptive Behaviour Scale help assess this progression quantitatively, cognitive endpoints alone have not reliably supported trial success.

Issues with trial participant availability

Typically, MPS CTs enrol children after diagnosis, when they are already below the normal developmental curve and showing behavioural issues that complicate reliable neurocognitive assessment. At this stage, returning a child to the normal developmental curve is unfeasible, but outcomes like stabilisation or slower decline are often as meaningful as improvements. However, trials may require 5–10 years to show clear evidence of a diversion from the disease natural history, making measurable benefit difficult to demonstrate.

Attempts to run trials with pre-symptomatic children have faced major challenges requiring global recruitment and the relocation of families, often with an older, severely affected child with complex medical needs. Newborn screening cannot take place until a therapy is available. Treating very young, presymptomatic patients requires even more time to show a clear divergence from the normal disease trajectory. As a result, many studies end not due

to lack of efficacy, but because the financial burden becomes too great for companies to continue.

A tale of CTs from University of Manchester UK: Past failed trials have taught us a lot about the role of HS

Intra-thecal ERT in MPSIIIA (SHireHGT/Takeda, 2010) Phase I/II trial, was an early study conducted when the understanding and measurement of HS were more limited [Wijburg F, 2013]. As IV enzyme could not cross the BBB, monthly intrathecal doses (10–90mg) were delivered directly to the CSF. Early assays lacked sensitivity and specificity and overestimated CSF-HS reduction, suggesting near-complete clearance and leading to likely suboptimal dosing intervals in the trial. Later data showed only a 60% reduction [Jones S, 2016]. Reliance on inaccurate BMs and neurocognitive endpoints contributed to trial failure, despite clinical benefit.

Success in CLN2 with Brineura (300mg biweekly) shows CNS enzyme therapy can work. More accurate BMs might have changed the outcome. In rare diseases, with few chances to succeed, dosing often depends on informed guesswork.

The Phase III academic trial of Genistein, a nutraceutical isoflavone, began in 2015 with limited UK funding [Ghosh A, 2021]. Many families were already accessing off-label Genistein online. Funding allowed the study to run for only two years and primarily enrolled older patients when other studies focused on a younger cohort, and cognitive testing proved unsuitable as an endpoint.

With no better options and potential risks from ongoing off-label use, the MHRA approved CSF HS as the primary endpoint. Despite high doses, CSF-HS was reduced by only 5.5%, showing no likely clinical benefit. Using CSF HS as a BM enabled the trial to end early, allowing families and researchers to focus efforts on more promising treatments.

PART 2 - WHAT DOES THE SCIENCE TELL US? (RATIONALE FOR HEPARAN SULFATE AS A BIOMARKER)

KEY MESSAGES: WHAT DOES THE SCIENCE TELL US?

- **HS drives CNS pathology:** Extensive historical, cross-species, and clinical evidence confirms a conserved link between HS accumulation and CNS pathology in neuronopathic MPS, with recent studies showing that reducing CSF HS strongly correlates with reduced brain storage and improved neurological outcomes
- **CSF HS is a CNS-specific BM:** Gene therapy studies in MPS IIIB mice show that only CNS-targeted treatment reduces brain and CSF HS, confirming that CSF HS originates from the brain and reliable BM of CNS disease and treatment response in neuronopathic MPS
- **Validated assays enable precise and accurate measurement:** Advanced assay techniques, using validated non-reducing end and internal disaccharide assays are both effective for diagnosis, newborn screening, and monitoring treatment response
- **Previous CTs have evidenced the utility of HS as a BM:** Multiple gene and enzyme therapy trials (e.g., UX111, RGX-121, tividenofusp alfa, OTL-201) show CSF HS reduction correlates with clinical benefit, including stabilisation or improvement in cognitive and functional outcomes and supports more efficient trial design
- **Call to action:** HS should be recognised as a toxic disease-causing metabolite and valid surrogate endpoint within regulatory frameworks to speed up access to life-saving therapies for patients with neuronopathic MPS
- **CT failure has significant impacts on researchers, patients and families,** and delays in treatment access have not been due to safety concerns but to regulatory and funding barriers. Earlier use of HS as a surrogate endpoint could have accelerated approvals

Development of heparan sulfate assays

Frits Wijburg (FW), Amsterdam UMC, Academic Medical Center

SUMMARY

- HS is a key GAG involved in **cell signalling** and **extracellular interactions**; when lysosomal enzymes fail to degrade it, HS accumulates and **disrupts cell processes**
- **Progressive neurodegeneration** occurs only in MPS types with **HS accumulation**
- HS in CSF can be **reliably measured** and followed up during the course of a CT
- Different **assays** are available, but both are **validated** and **highly sensitive** for BM analysis in trials
- **Change in HS in CSF is related to clinical response -** HS reduction response is rapid (months) but clinical response may take years to demonstrate

- HS in CSF is an ideal BM to assess **early treatment response** in neuronopathic mucopolysaccharidosis (Hurler, Hunter, Sanfilippo and Sly disease)

A note on nomenclature: HS is one of the GAGs which is also named mucopolysaccharide

HS is one of four types of sulfate sugars found in GAGs, alongside dermatan sulfate, keratan sulfate, and chondroitin sulfate. These are long chains of repeating disaccharides, each defined by distinct sugar structures and sulfation patterns. They reside as 'antenna' on the cell surface and couple with proteins to form proteoglycans, capturing molecules in the extracellular matrix. GAGs are essential for normal cell function, acting as coreceptors for several growth factors, aiding signal transduction and sequestration of extracellular humoral factors. GAGs are normally broken down in the lysosome through stepwise degradation starting from the non-reducing end (NRE), requiring specific enzymes. When these enzymes are missing or faulty, HS accumulates, disrupting cell progresses and leading to disease. Different enzyme deficiencies result in different MPS types.

Progressive neurodegeneration occurs only in MPS types where HS builds up, MPS I (Hurler), MPS II (Hunter), MPS III (Sanfilippo), and MPS VII (Sly), meaning that HS is the key driver of brain disease.

Before 2015, GAG concentration was measured using dye-binding and electrophoresis methods, which lacked sensitivity. Now, advanced techniques like liquid chromatography–mass spectrometry (LC-MS) provide sensitive and specific GAG detection and quantification.

Analytical approaches for measuring HS in biological fluids (blood, urine and CSF):

1. **Non-reducing end (NRE) assays** – Detect specific disaccharides in the NRE of the accumulating HS. These are highly sensitive and specific, useful for differential diagnosis and newborn screening using dried blood spots
2. **Internal disaccharides assays –** More widely used, this method enzymatically digests the entire molecule to measure various disaccharides. It is also sensitive and specific, and effective in identifying specific MPS types in newborns

Both methods are validated for CSF HS measurement and have been used as outcome measures in several treatment trials in neuronopathic MPS II and MPS III with some cases demonstrating reductions of over 90% in CSF HS levels.

Determining the origin of CSF heparan sulfate using biological compartment specific gene therapy

Grant Austin (GA), Washington University School of Medicine, Department of Pediatrics, USA

SUMMARY

- **Neuronopathic MPS lacks therapies to target the CNS**, and slow neurocognitive clinical changes make CTs challenging
- Gene therapy experiments in MPS IIIB mice using CNS-only (AAV9) vs. peripheral-only (AAV7) delivery of an intracellular enzyme confirmed:

    - Only CNS-directed treatment reduced brain and CSF HS and markers of neuroinflammation
    - Peripheral treatment reduced serum HS but not CSF or brain HS
- These results confirm that **CSF HS originates from the brain** validating it as a **specific and reliable BM of CNS disease and treatment response** in neuronopathic MPS

GA summarised work to determine where CSF HS originates from and whether it is a marker of neurologic disease. CSF HS correlates with brain HS in animal models (mice, dogs) [Austin et al, in preparation; Dickson PI, 2012] but also shows some correlation with peripheral HS [Dierenfeld AD, 2010; Vera MU et al, 2020] raising questions about the origin of CSF HS. In MPS patients and dogs treated with IV therapy, brain GAGs decreased, and CSF HS reductions mirrored those in serum. One hypothesis suggests CSF HS comes from the brain, supporting its use as a CNS BM and implying some BBB penetration by IV therapy, at least in MPS I. Alternatively, researchers considered that CSF HS may partially come from the bloodstream, making it less reliable for CNS monitoring.

To explore the origin of CSF HS, researchers used compartment-specific gene therapy in MPS IIIB mice. The therapy used NAGLU, the deficient enzyme in MPS IIIB, linked to LAMP1, a non-secreted lysosomal membrane protein, ensuring enzyme activity remained intracellular [Mikulka CR, 2020]. Tissue-specific targeting was achieved using viral vectors: AAV7, which does not transfect the CNS, delivered LAMP1-NAGLU via IV to treat only peripheral tissue. AAV9, combined with a CNS-specific promoter, was used to target the CNS tissue exclusively.

Enzyme activity assays confirmed tissue-specific delivery:

- **AAV7 (peripheral):** NAGLU activity was detected in peripheral tissues but not in the brain or serum
- **AAV9 (CNS):** NAGLU activity was seen only in the brain, with no activity in peripheral tissues or serum
- Only CNS-targeted treatment (AAV9) reduced brain HS, CSF HS, and markers of neuroinflammation. Peripheral treatment (AAV7) had no effect on the brain or CSF HS, though serum HS was reduced

Findings confirm that:

- Gene therapy can be precisely targeted to specific compartments using appropriate vectors and promoters
- Tethering enzymes to LAMP1 ensures intracellular action
- CSF HS is a valid and specific BM of CNS disease in MPS IIIB and does not reflect peripheral HS levels
- CNS-directed intracellular therapy is disease-modifying in MPS IIIB mice

These animal models have shown that if the brain is not treated, there is no reduction in HS in the brain. Since CSF HS is a marker of this reduction, it would be a good BM to measure the impact of treatments on the brain.

Comparative and preclinical medicine

Matthew Ellinwood (ME), National MPS Society, USA

SUMMARY

- **CSF HS is strongly correlated with CNS HS and neuropathology.** Data from animal and human studies consistently show that CSF HS levels reflect brain HS storage, neuroinflammation, tissue pathology, and behavioural outcomes
- **The neuropathological role of HS is evolutionarily conserved. HS accumulation** leads to **CNS degeneration** in all MPS types with primary **HS storage** (MPS I, II, III, VII) and across multiple mammalian species
- **Therapeutic studies support CSF HS as a valid CNS BM.** In MPS IIIB canine models and MPS IIIB patients, intrathecal ERT reduced CSF and brain HS levels, prevented atrophy, improved behaviour, and demonstrated a **clear dose-response relationship**

The link between HS and neuropathology has long been recognised:

- In 1964, a study identified a new form of MPS (Sanfilippo) with nervous system degeneration and excess excretion of HS only [Terry K, 1964]
- In 1973, elevated CSF HS levels in MPS III were linked to mental retardation, reinforcing the connection between HS accumulation and neurological decline [Dekaban AS, 1973]

This association is biologically conserved:

- MPS types with primary HS accumulation (MPS I, II, IIIA–D, VII) are neuronopathic, while those without are not
- All mammalian models with HS accumulation (e.g. bovine, canine, feline) show neuropathology
- MPS IIIB is found in six species, reflecting a conserved neuropathological role of HS across 310 million chronological years and 927 million years of evolutionary time

A Phase I/II study in MPS IIIB patients [Muschol N et al., 2023] used intrathecal ERT, injecting tralesinidase alfa directly into the CSF, similar to Brineura for CLN2 Batten disease. Preclinical studies in canine MPS IIIB [Ellinwood NM, 2022] used intraventricular/ intracisternal delivery to bypass the BBB. A dose of 12mg or 48 mg of tralesinidase alfa (a form of NAGLU) was given in an artificial CSF vehicle for 42 infusions over 20 months. Both doses showed strong CSF and CNS tissue GAG correlation, and the 48 mg dose effectively eliminated HS storage confirming a strong association between CSF and CNS HS levels.

Cerebellum-targeted studies showed a dose-dependent response in both tissue and behaviour over time. The study followed a preventative model, treating animals before disease onset. Treated animals had elevated mean diffusivity, which normalized with increasing doses and showed strong preservation of cerebellar rebound function and successfully completed T-maze reversal learning, unlike untreated controls.

The role of heparan sulfate in advancing clinical trial development

David Whiteman (DW), MPS Society, CSAC

SUMMARY

- **HS** has been shown to be a **toxic metabolite** and **key disease driver** in neuronopathic **MPS II and III,** directly **linked to CNS damage**. Its reduction is strongly associated with clinical benefit
- Early use of **HS as a surrogate BM** could have enabled **earlier** and broader **access** to treatments like IV and IT **idursulfase,** generating **long-term real-world data** while benefiting patients
- Delays in access were not due to safety or efficacy concerns
- **CT design challenges**, including appropriate **endpoint selection**, **regulatory demands**, and **commercial pressures,** particularly affect small biotech companies, many of which **cannot sustain decade-long studies** without revenue, limiting treatment progress
- Endpoint selection is often influenced by commercial or regulatory pressures, not always aligned with patient benefit or feasibility

GAGs are long-chain molecules broken down by a series of enzymes. If the first enzyme fails, the rest can't function, leading to GAG buildup. At the time of this study, only total (mainly urinary) GAGs could be measured.

Idursulfase IV development history [Whiteman DA, 2017]

1917	Hunter syndrome was first defined in clinically by Charles Hunter
1973	Biochemical basis of Hunter syndrome was established with the discovery of a Hunter-corrective factor, now known as iduronate-2-sulphatase (I2S).
1973-	Further clinical delineation of MPS II
1983	Further delineation of the natural history of MPS II
1988	Transkaryotic Therapies (TKT) were formed to develop genetic therapies based on gene conversion and developed methods that allowed them to manufacture a number of recombinant human enzymes.
1993	I2S gene cloned
1993	Expression of recombinant human I2S
1993	TKT began pre-clinical development of a recombinant human I2S (know as DRX006A)
2001	Phase I CT (TKT008) of idursulfase confirmed rapid (2 week) urinary GAG reduction in MPS II patients treated with idursulfase in dose-dependent curves

It was at this point that regulatory approval could have been sought based on BM responses, but it took another five years for marketing authorisation.

2003–2005	Phase II/III "registration" trial • Confirms the uGAG finding in a larger group of patients with wider age range. • Improvements in 6-minute Walk Test and in pulmonary function • Statistical success on a combined endpoint analysed by non-parametric methods
2006	Marketing authorization granted by US FDA
2007	Marketing authorization granted by EMA

Further development history

2007	Hunter Syndrome Outcome Survey (HOS) confirmed and expands clinical findings (both in natural history of MPS II, and in response to treatment, including demonstration of a survival benefit
2012	Study of MPS II boys who suffered administrative withdrawal of previous idursulfase therapy showed rapid re-accumulation of uGAG and deterioration in clinical findings

Reflecting on 25 years of clinical trials and real-world experience in MPS II, a toxin/biomarker approach could have enabled safe and broader access to idursulfase for children and adults to treat the somatic symptoms of the condition as early as 23 years ago. Likewise, a toxin/BM approach could have made idursulfase-IT safely available to children as early as 13 years ago. Not only would that access have been considered beneficial by the families and children, but a definitive answer to clinical efficacy and safety over the longer time period needed, in a real-world setting, could have been obtained.

Impact of trial failure on clinicians and patients

Spyros Batzios (SB), Great Ormond Street Hospital, London, UK

SUMMARY

- Up to **one third of paediatric CTs fail**, with **85% due to preventable reasons** such as **financial strain**
- **Trial discontinuation** causes deep **psychological distress** for families and research teams, breaking trust and hope, and raising concerns about the sustainability of future research
- **Example**: A promising Phase I/II trial for tralesinidase alfa in MPS IIIB was abruptly terminated due to lack of regulatory approval and funding, despite early positive BM and clinical data. The decision left patients and families in distress and fearful for their child's health as treatment was withdrawn
- **Early BM-based trial design, better communication, and patient stratification can reduce trial failure**
- Sponsors must **prioritise patient wellbeing** and follow through on trial commitments; **informed consent is a moral contract, not just a legal one**

CTs may fail for valid reasons such as lack of efficacy or safety concerns, but many failures are avoidable. One study [Pica N, 2016] found that 1 in 5 paediatric CTs fail, most commonly due to patient accrual (36.5%), conduct problems (12.5%), or termination due to lack of efficacy or safety (12.5%). However a more recent meta-analysis [Speich B 2024] showed that 1 in 3 paediatric CTs fail, with 85% failing due to preventable reasons, including financial hardship.

Financially driven trial discontinuations have been a longstanding issue. A real-world example is the discontinuation of a Phase I/II trial investigating intracerebroventricular tralesinidase alfa in MPS IIIB [Muschol N, 2023]. This well-designed trial incorporated clinical, neurological, and BM (HS) outcome measures and showed promising early data. Despite this, the trial was abruptly terminated after the sponsor failed to secure regulatory approval and further funding to comply with requests for additional clinical data. A sudden unexpected instruction was issued via email to halt all trial activities, described by SB as 'the worst email of my career so far'. The company had already discontinued treatment for one patient as they did not fill cognitive criteria despite notable improvements and the second was under general anaesthesia for assessments when the termination notice arrived.

Healthcare professionals report feeling shock and extreme sadness when CTs are terminated, as it means withdrawing the hope of treatment from patients and families. The emotional burden is compounded by frustration toward sponsors, which can be difficult to manage while maintaining professionalism. Close relationships developed through long-term care are disrupted, and handing care back to local teams is often painful. There is also concern that future trials may be delayed or cancelled as a result.

The discontinuation of CTs exerts a significant psychological impact on parents who describe severe mental anguish and difficulty coping. Fragmented communications from sponsors adds to uncertainty and fear and some children even question whether they did something wrong to cause the trial to end.

The impact of failed trials on both professionals and families is profound. Given that 85% of paediatric CT failures are preventable, efforts must be made to reduce this rate through earlier identification of promising drug candidates, better patient stratification, prioritising BMs as outcome measures, leveraging big data and diversifying results.

Importantly, sponsors carry ongoing responsibility to act in the best interest of the patient and to complete the trial unless safety or efficacy concerns demand otherwise. Informed consent is not just a legal formality, it is a moral contract.

Panel discussion

(David Whiteman (DW), Frits Wijburg (FW), Grant Austin (GA), Matthew Ellinwood (ME), Spyros Batzios (SB))

SUMMARY

- **HS is a strong, disease-relevant BM in MPS, as it causes pathology and its reduction prevents progression**

- CSF HS is a useful **early indicator,** especially in pre-symptomatic disease; cognitive endpoints should be used alongside BM data
- **Assay consistency is key** but either enzyme- or methanol-based methods are suitable
- MPS IIIB trial ended due to a **lack of funding**, **not efficacy,** despite HS being accepted as a BM

1. Most CTs measure disaccharides which require an extra processing step. There are **two methods of measuring** the disaccharides by mass spectroscopy; either digest with methanol, or with an enzyme. There is **no advantage of one method over another**, but it is important that the same method is used throughout the study.
3. **The most important criteria to determine the clinical relevance of a BM in MPS** is whether it causes the disease and whether its elimination prevents the disease. In the case of HS, it causes the disease and its elimination prevents it.
4. **To determine if patients with normal HS levels still qualify for CTs**, it is important to know if the patient is suffering from the neuronopathic phenotype of the disorder, which can be done either based on genetic analysis, clinically, family history or a combination with increased HS in CSF.
5. **The MSP IIIB trial failed or did not result in an approved therapy** because the economic burden of running an additional CT for another three to five years was too big; the company could not raise the capital. The company were given the opportunity to use HS but were still unable to raise the capital at this point.
6. **It is fair to think of HS as a toxic metabolite of cognitive disease if pre-symptomatic.** If using CSF as an absolute measure, HS is a good BM to use.
7. **Cognitive measures should be used** since they are well recognised, but **in addition to other measures** such as the effect on BMs.

PART 3 – CURRENTLY ACCEPTED AND EVOLVING EVIDENCE

KEY MESSAGES: CURRENTLY ACCEPTED AND EVOLVING EVIDENCE

Results from completed and ongoing CTs confirm CSF HS as a disease-driving, actionable biomarker

- **DNL310 (MPS II):** An ERT able to cross the BBB, showed >90% CSF HS and >80% urine HS reductions which correlated with sustained clinical outcomes including improvements in cognition, hearing, liver volume
- **RGX-121 Gene therapy (MPS II):** Saw dose dependent reductions with a mean of 86% in CSF HS D2S6 and neurocognitive stabilisation or gain. Supports use of CSF HS D2S6 as a surrogate endpoint though variability in baseline function complicates outcome assessment
- **UX111 Gene therapy (MPS IIIA):** AAV9 gene therapy reduced CSF HS by up to 79% correlating with clinical outcomes, early treatment led to cognitive gains and post symptomatic treatment led to the maintenance of skills meaningful to caregivers (e.g. ambulation, feeding and communication). CSF HS was predictive of outcomes and flagged immune responses
- **OTL-203 (MPS IH) & OTL-201(MPS IIIA):** HSC gene therapies showed sustained enzyme activity, HS clearance, and age-appropriate cognitive development in most patients in MPS-IH, supporting further development in MPS IIIA

The panel concluded that CSF HS is a proximal, CNS-specific BM reflecting disease burden and treatment response and supports more efficient trial design. A 50% reduction is likely clinically meaningful

Tividenofusp alfa (DNL310) clinical trial for MPS II

Carole Ho (CH), Denali Therapeutics

SUMMARY

- **Tividenofusp alfa**, a novel **ERT** designed to **cross the BBB**, was well tolerated and showed **robust and sustained reductions** and **normalisation in CSF HS (>90%)** and **urine HS (>80%),** even in patients previously on standard ERT. Normalization in Neurofilament (NfL) seen within 2 years
- **BM reductions correlated with improvements in both peripheral and CNS clinical outcomes** including liver volume, hearing, cognition, and adaptive behaviour
- **Urgent need:** Patients continue to die from toxic HS accumulation in the CNS despite scientific clarity on CSF HS as a BM
    - The **disease biology is clear** and after over a decade of research, it is clear **CSF HS is a toxic, disease-driving BM that directly reflects CNS pathology**
    - **Validated, sensitive assays** are available and **reductions in CSF HS are reasonably likely to predict clinical benefit,** with emerging therapies also showing correlated improvements in secondary markers like NfL

Tividenofusp alfa is a novel ERT engineered to cross the BBB via a transferrin receptor binding site to the FC portion of a fusion protein. Through weekly IV infusions it delivers the missing MPS II enzyme both to peripheral tissues and the brain, addressing unmet needs in both compartments. Once across the BBB, the low pH environment releases the drug, allowing broad distribution to neurons and glial cells affected by the disease.

A multicentre, open-label Phase I/II study in 47 (41 patients continue in the trial) paediatric MPS II patients (ages 3 months to 12 years) was conducted across the UK, Netherlands, Canada, and the USA, and will support accelerated approval in the USA. Primary endpoint is at 24 weeks and also includes a safety extension and an open-label extension.

Patients included treatment-naïve individuals and those switched from standard ERT without washout. Median follow-up is 2 years, with data available up to 4 years.

- **Dosing:** Up to 30 mg/kg was tested. 15 mg/kg was selected as the safe and efficacious dose. No dose-limiting toxicities were observed
- **Safety:** Most common AEs were infusion-related reactions (IRRs) and anaemia (managed with iron). The number and intensity of IRRs decreased over time
- **CSF HS:** >90% reduction seen by week 24 ($p < 0.0001$), patients achieved normal levels which were sustained through week 153
- **Urine HS:** >80% reduction, even in patients previously on standard care, none of whom had normal urine HS at baseline ($p < 0.0001$) suggesting an unmet medical need even in the periphery with standard care

NfL has emerged as an important BM reflecting severity, prognosis and treatment response in several neurologic diseases.

- In multiple sclerosis, SMA, CLN2 and also ALS
- A 2025 publication (Argueta C, 2025) shows that NfL is correlated with disease severity and clinical outcomes in MPS II

- **NfL** Significant and sustained reduction over time ($p < 0.0001$ at week 153), with >70% of patients achieving normal levels after 2 years
- **Hearing:** Statistically significant improvements seen in hearing thresholds from week 24 onwards, suggesting improved hearing which could be a combination of both central and peripheral effects
- **Liver volume:** Normalized in all patients by week 24 and week 49, including treatment-naïve patients who showed rapid reduction at least equivalent to standard of care
- **Cognition and adaptive behaviour:** Statistically significant gains seen in cognitive (Bayley scores) and adaptive behaviour (Vineland) scores starting at week 49, suggesting ongoing developmental progress that usually would not be expected in patients at this age

The use of heparan sulfate as a surrogate biomarker in MPS II as part of investigational RGX-121 Gene Therapy Program (CAMPSIITE® Phase I/II/III)

Nidal Boulos (NB), Regenxbio

SUMMARY

- RGX-121(clemidsogene lanparvovec), a gene therapy for neuronopathic MPS II (Hunter syndrome), showed **favourable safety** and **sustained CSF HS D2S6 reductions** (up to 86%) across 25 patients, with **developmental skill acquisition** observed up to four years post-treatment
- The CAMPSIITE trial demonstrated **dose-dependent BM response** and **neurodevelopmental stabilisation or gains**, especially when treatment was given early
- A rolling Biologics License Applications (BLA) was initiated in Q3 2024 under the **accelerated approval pathway**, using **CSF HS D2S6 as a surrogate endpoint**
- CSF HS D2S6 is a **mechanistically relevant BM** reflecting CNS disease activity and early therapeutic response
- Interpretation of clinical outcomes is challenging due to **variability in baseline function** and disease progression and **slow divergence from natural history**

Neuronopathic MPS forms are characterised by elevated HS levels in the brain leading to CNS abnormalities and neurocognitive impairment. Newborn screening for MPS II allows for early identification and treatment of patients before onset of symptoms. However, determining pathogenicity of variants is complex, and newborn screening is limited by uncertain enzyme thresholds and variability in enzyme activity measurements. Measuring GAGs, particularly HS is a more reliable BM than enzyme activity.

The CAMPSIITE trial

CAMPSIITE is the clinical study evaluating RGX-121, a one-time gene therapy designed to deliver a functional copy of the IDS gene directly into the CNS to restore enzyme activity in neuronopathic MPS II patients.

- **Part 1(dose-finding phase):** Assessed safety as the primary endpoint, using a dose-escalation design. The secondary and exploratory endpoints included the surrogate BM D2S6, neurodevelopment assessments (Bayley Scales), caregiver reported outcomes, systemic BMs (urine and plasma GAGs) and ERT-free status
- **Part 2 (pivotal phase):** Primary endpoint was the proportion of patients with CSF D2S6 below maximum attenuated level at week 16. Secondary and exploratory endpoints included Bayley Scales, caregiver reported outcomes, brain MRI, safety and systemic BMs (I2S, GAGs)

A total of 15 severe (neuronopathic) MPS II patients aged 4 months to over 5 years were enrolled in Part 1 across three dose levels. Ten patients in the same age range were enrolled in Part 2.

The study used CSF levels of the HS disaccharide D2S6 as a surrogate endpoint reasonably likely to predict clinical benefit

- HS D2S6 contains 2-sulfate on non-reducing ends which are cleaved by I2S and therefore reflects I2S enzymatic activity
- Elevated CSF D2S6 levels correlate with CNS pathology in neuronopathic MPS II, distinguishing it from attenuated forms
- Validated assays can accurately quantify levels of D256 in CSF

Clinical data/outcomes

- **Safety:** RGX-121 was well tolerated at all dose levels.
- **BM response:** In phase 1, dose-dependent CSF HS D2S6 reductions were seen. At dose level 3 (carried forward to pivotal trial), reductions approached 86%. One rebound (dose level 1) was unrelated to the drug. In phase 2, eight of ten patients met the threshold of CSF HS D2S6 below the maximum attenuated level at week 16 (p=0.00016); the other two showed reductions of 55% and 85% (Mean reduction: 86% at week 16)
- **Neurodevelopment:** In phase 1, most patients stabilized or gained skills. Consideration of baseline functioning is key; higher-functioning patients (with 2SD of normal function) maintained within functioning 2 standard deviations of normal and continued acquiring skills; for more impaired patients (functioning below 2SD from normal) stabilization or maintenance of existing skills is meaningful. Treatment response will be dependent on the extent of the neurological deficit at baseline

Treatment with UX111 gene therapy rapidly reduced heparan sulfate exposure in cerebrospinal fluid and improved long-term cognitive function in children with mucopolysaccharidosis IIIA (MPS IIIA)

Heather Lau (HL), Ultragenyx

SUMMARY:

An AAV9-based IV gene therapy targeting both CNS and peripheral tissues was developed in academia and advanced by Ultragenyx with a rolling BLA submitted in Dec 2024

- UX111 led to **substantial and sustained reductions** in **CSF HS** in all patients (up to 79%) over time, **irrespective of age or stage of disease progression** at the time of treatment with biochemical efficacy observed as early as six months post-treatment
- **CSF HS levels correlated with clinical outcomes**, predicting cognitive changes and flagging immune responses before clinical decline
- Younger patients (treated before cognitive decline) showed **long-term cognitive and functional gains** compared to natural history; in older patients, benefits included meaningful **maintenance in daily function**
- **CSF HS reduction of >50% correlated with cognitive stabilisation**

Children with MPS IIIA accumulate toxic HS from birth, despite appearing developmentally normal, with clinical manifestations appearing after 24 months. CSF HS is regarded as the primary disease activity BM in neuronopathic MPS providing an early indicator of treatment response or failure before clinical changes are evident and can be assessed.

UX111 gene therapy

UX111 is an IV-delivered AAV9 gene therapy for children with MPS IIIA, designed for peripheral and CNS expression via a ubiquitous promoter. AAV9 crosses the BBB and the treatment leverages both direct neuronal transduction and cross-correction to restore enzyme functioning and rescue cells from toxic GAG accumulation.

UX111 was originally developed in academia and progressed through an open-label Phase I/II and Phase III dose-finding study. It was later advanced by Abiona generating substantial data, including a pivotal 24-month trial with 17 patients and a long-term follow-up study now reaching six years. In March 2022, Ultragenyx assumed the program after Abiona was unable to. A rolling BLA was submitted in December 2024.

27 patients originally received the proposed registrational dose; the cohort was slightly older than the target population. No placebo group was used; outcomes were compared to published natural history data. The program now includes nine years of data, with biochemical efficacy observed as early as six months post-treatment.

BM response and clinical outcomes

Rapid and sustained reductions in CSF HS were observed over 7–77 months. All patients showed a response; over 80% showed reductions in CSF HS of over 50% with a maximum reduction of around 79%. CSF HS was also predictive: two patients with immune responses to treatment showed BM rebound before clinical decline, followed by recovery post-treatment.

Retrospective reviews of neurocognitive assessments showed a clear separation for younger patients (treated prior to decline) in cognitive, communication, and fine motor development from natural history controls, but this was only evident after 5 years. In older, more advanced patients, clinical benefit is more difficult to assess and will look different; maintenance was seen in domains meaningful to caregivers including communication, ambulation, and self-feeding abilities. A reduction of over 50% in CSF HS significantly correlated with stabilisation of improvement in cognition. All patients experienced treatment-emergent adverse events (TEAEs), but none led to death or discontinuation. All AEs were mild to moderate and resolved spontaneously.

Clinical evidence OTL-201 - HSC-GT approach, proof of concept in neurometabolic disorders and OTL-201 registrational study design

Leslie Meltzer (LM), Orchard Therapeutics

SUMMARY

- Orchard Therapeutics is developing gene therapies using **autologous haematopoietic stem cells (HSCs) to treat LSDs**

- Proof of principle established in metachromatic leukodystrophy (MLD), where modified HSCs cross the BBB, deliver enzyme activity to the CNS, and provide durable, clinically meaningful benefits (OTL-200)

- **OTL-203 (Phase 1/2 trial; MPS-IH):** Interim neurological outcomes in show that HSC gene therapy leads to **sustained enzyme activity**, **CSF clearance of HS** and **dermatan sulfate**, normalised growth, improved joint and motor function, and age-appropriate cognitive development in most patients, supporting its potential as **a durable and novel CNS-targeted treatment**
- **OTL-201 (R119861; Phase I-II; MPS-IIIA): Promising early results in MPS-IIIA,** with **HS clearance and cognitive improvements** in 4 of 5 treated patients support progression toward registrational trials

Orchard Therapeutics is developing gene therapies using autologous HSCs to treat genetic disorders, particularly LSDs. Their approach harnesses the self-renewing capacity of HSCs to provide a durable supply of genetically corrected cells following a single administration. Patient-derived HSCs are genetically modified with an integrating vector along with other emerging modalities and are reintroduced following an autologous bone marrow transplant (BMT) (which reduces risk and maintain or even improves efficacy as compared to allogenic BMTs). These cells give rise to the entire haematopoietic lineage including monocytes and macrophages that can cross the BBB infiltrate affected tissues, including the CNS, where they differentiate into microglial-like cells and by super-physiological expression of the enzyme of interest they can cross-correct the unmodified neurons and other CNS cells.

Proof of principle for this approach was established in metachromatic leukodystrophy (MLD), a lysosomal storage disorder marked by toxic sulphatide accumulation in the CNS. In MLD, the therapy demonstrated statistically significant and clinically meaningful benefits compared to natural history (OTL-200) [Fumagalli et al, 2025].

OTL-203 Ph 1/2 Trial in MPS-IH: Interim neurological outcomes

Building on the success of the HSC gene therapy approach in MLD, OTL-203 is being evaluated for MPS-IH, where the current standard of care (ERT and allogeneic BMT) leaves residual disease, particularly in neurocognition, skeletal health, and joint mobility. The ability of modified haematopoietic stem cells to migrate to affected tissues and the CNS offers a potentially more effective and durable therapeutic option.

Early BM data show enzyme activity and CSF clearance of dermatan sulfate and HS, supporting CNS efficacy. In an ongoing study of 8 patients followed for up to 5 years (a time point at which patients on the allogenic BMT would start to fall of the normal growth curve), participants have maintained normal growth, with improvements in joint mobility, motor scores, and radiographic imaging. CNS outcomes also improved; seven of eight have achieved age-appropriate cognitive development; the eighth, whose participation in neurocognitive assessments is limited by a behavioural disorder, is showing progress in all other clinical domains. Brain MRI improvements continue across all patients.

OTL-201: Proof of Concept: Overview of the study R119861 for Sanfilippo syndrome type A (MPS-IIIA)

OTL-201 is being evaluated in collaboration with the University of Manchester in a Phase I/II study for MPS-IIIA, a condition with no benefit from allogeneic transplant and high unmet

need. The therapy uses autologous haematopoietic stem cells modified to overexpress SGSH. Five non-UK patients treated in 2020–2021 are being followed. Results show SGSH activity in both CSF and periphery, with clearance of HS in the plasma and CSF. Four of five patients have shown continued cognitive improvement, progressing from Bayley to Kauffman assessments, unprecedented in this population. Developmental gains include speech acquisition, continence, complex play, improved behaviour, quality of life and participation in daily living. Results from this ongoing study supports advancement toward registrational trials.

Orchard is developing a single globally harmonised protocol for a registrational trial in MPS IIIA, aiming to streamline global regulatory approval. CSF HS is proposed as the primary surrogate endpoint, reasonably likely to predict clinical benefit. **Given the high unmet need and lack of treatment options, a faster path than the decade-long MLD development is necessary.**

Panel discussion

(Carole Ho (CH), Heather Lau (HL), Leslie Meltzer (LM), Nidal Boulos (NB))

SUMMARY

- **CSF HS** is a **biologically relevant** and **proximal BM** for neuronopathic MPS, **directly reflecting substrate accumulation** due to enzyme deficiency and providing a clear indicator of disease burden and therapeutic effect in the CNS
- **CSF HS a mechanism-based BM** for MPS, unlike generic markers like NfL, which reflect neuronal damage but not the root cause
- While **thresholds are difficult to define**, around a **50% reduction in CSF HS** is likely **clinically meaningful**
- HS CSF is the **best available indicator of CNS pathology**, as brain biopsy is not feasible
- CSF HS has also helped **identify early immune responses**, supporting **timely intervention** in the UX111 gene therapy CT

1. **What are the limitations of CSF HS as a BM?**

   The panel acknowledged both the promise and limitations of CSF HS as a BM in neuronopathic MPS.

   LM: Orchard is currently at the beginning of journey of using CSF HS as a BM; MLD took 15 years from initial treatment to approval as it was conducted without a BM.

   CH: Emphasized that CSF HS is biologically relevant as it directly reflects the missing enzyme's substrate, making it a strong proximal BM. However, she highlighted the difficulty of evidencing statistically significant correlations between BM data and clinical outcomes due to the small patient populations, disease heterogeneity, and limited ability to stratify by baseline.

HL: It is a fatal disease, specific measures are not needed to show benefit in this regard demonstrating a reduction in CSF HS levels could justify accelerated approval, with clinical benefit assessed through long-term follow-up

2. **Is there a threshold to reach in CSF HS reduction and what do we need to achieve?**

   HL: While defining an exact threshold is challenging due to small patient numbers, reductions over 50% can be considered meaningful in this fatal disease. Reductions aren't immediate, but any clear decline is important. As brain biopsy isn't feasible, CSF remains the best indicator of CNS substrate levels.

3. **Why CSF D2S6 and not total disaccharides for end points?**

   NB: While both are measured, D2S6 was prioritised as it can distinguish between severe and attenuated MPS II. The limited MPS II CSF samples indicated that reducing D2S6 to attenuated levels provides a treatment response, and while total disaccharides also declined, D2S6 is more sensitive in the CSF.

4. **Why is NfL not used as a BM?**

   CH: In monogenetic diseases with a known enzyme deficiency, measuring the specific substrate is more useful. Earlier BMs can guide dosing and demonstrate early clinical benefit. While NfL may be useful in the future, more understanding is needed before it can support treatment development in this context.

5. **Antibodies to the enzyme – are they measured in the blood or the CSF? Did you follow up on all patients in order to start immunotherapy?**

   HL: Antibodies were monitored in both blood and CSF. Immune response tracking was implemented with a protocol amendment following sponsor transition, only one patient has required intervention so far. Most immune responses appear within 6–18 months, with the goal of achieving tolerization. **CSF HS proved helpful in signalling early issues, enabling timely response.**

PART 4 – VIEWS FROM THE REGULATORS

KEY MESSAGES: VIEWS FROM THE REGULATORS

- **Clinical Trial Challenges in MPS:** Small ultra rare population (fewer than 500 severe MPS patients in the US), delayed diagnosis, and irreversible neurodegeneration, making long, placebo-controlled studies unethical and unfeasible. Disease stabilisation should be considered a meaningful outcome
- The Reagan-Udall Foundation's 2024 workshop explored the use of BM in rare disease regulation with a focus on CSF HS in neuronopathic MPS and highlighted the importance of cross-sector collaboration to advance BM-driven approvals and accelerate access to treatments
- **FDA** supports early BM use to enable access, with longer-term confirmatory data. CSF HS meets criteria for accelerated approval in MPS when paired with clinical trends and has allowed three BLA submissions using CSF HS as a primary BM.
- **CHMP/EMA:** Emphasises that while CSF HS is promising, it is not yet sufficient for standalone approval; robust clinical endpoints, clinically meaningful endpoints remain essential in MPS trials however the totality of evidence is important for regulatory decision making
- **MHRA:** Supports flexible regulatory approaches for rare diseases like MPS, and validated BM may be accepted as surrogate endpoints if strongly predictive of clinical benefit; less-validated BMs may be considered (e.g. conditional approval or EAMS) if a positive benefit-risk is demonstrated
    - Upcoming 2025 guidance will support the use of historical and real-world data as external controls
    - Both CHMP/EMA highlighted the importance of assay validation and encouraged developers to utilise alternative approval pathways and engage with regulators early emphasising that higher risk can be tolerated in rare conditions with high unmet need such as MPS

10 REASONS TO USE CSF HS IN ACCELERATED APPROVAL PATHWAYS
(JM- Presenter's own opinion)

1. Neuronopathic MPS are ultra-rare
2. The biochemistry of MPS is well understood
3. The primary event in neuronopathic MPS disorders is a defect in glycosaminoglycan metabolism giving rise to intra-lysosomal substrate accumulation and lysosomal dysfunction
4. CSF HS is always elevated in neuronopathic MPS sufferers
5. CSF HS can be reliably measured
6. CSF HS levels correlate with brain tissue HS in animal models
7. Reduction of CSF HS reflects a reduction in brain tissue HS
8. Reduction of secondary disease activity BMs of lysosomal dysfunction and neuronal injury support the relevance of CSF HS as the primary BM
9. Placebo-controlled trials are unethical in progressive and irreversible brain disease
10. Regulatory flexible is needed now to bring treatments to individuals with MPS

Overview and outcomes from the Reagan Udall Foundation public workshop

Susan Winckler (SW), Reagan-Udall Foundation for the FDA, USA
Joseph Muenzer (JM), University of North Carolina at Chapel Hill, USA

SUMMARY

- The **Reagan-Udall Foundation's 2024 workshop** focused on **BM in rare disease regulation**, using CSF HS in neuronopathic MPS as a case study and uniting FDA, academia, industry, and patient groups
    - **Key takeaway: Cross-sector collaboration** and **patient-focused development** are vital to accelerate innovation and improve access through **accelerated approval pathways**, with **post-approval studies** supporting long-term benefit confirmation

CT challenges in neuronopathic MPS

- **Small population** with fewer than 500 severe MPS patients in the US
- **Symptom onset** and hence **diagnosis** is **typically delayed** by which point significant damage has occurred
- **Long trials** are needed to show benefit
- **Placebo controlled trials** are **unethical** in this context

CSF HS is a reliable BM of CNS disease

- **CSF HS serves as a more reliable BM than serum enzyme levels:** it closely correlates with brain HS and rapidly reflects neuronal changes due to its high turnover and lysosomal specificity
- **FDA has allowed BLA submissions using CSF HS as a primary BM;** Ultragenyx UX111(MPS IIIA; priority review by august 2025), Regenxbio RGX-121 (MPS II; submitted March 2025), Denali Therapeutics Tividenofsup alfa (MPS II, submission expected early 2025)
- **Regulatory flexibility is needed now to bring treatments to patients with neuronopathic MPS**

THE MODERATOR'S PERSPECTIVE (SW)

In February 2024, the Reagan-Udall Foundation for the FDA hosted a public workshop focused on the use of BMs to support regulatory pathways in rare diseases, with HS in neuronopathic MPS highlighted as a case study. The Foundation, created by U.S. Congress to foster engagement between the FDA and external stakeholders, designed the event in collaboration with both FDA and non-governmental experts.

The workshop brought together representatives from the FDA, academia, industry, and patient organisations and aimed at sharing knowledge to understand how BMs can support accelerated approval in rare genetic diseases with an emphasis on the importance of post-approval studies to confirm clinical benefit.

The event succeeded in promoting cross-sector learning, with discussions spanning analytical validation, BM precision, and patient-centric development. A key takeaway was that collaborative efforts can drive innovation and help shorten timelines for bringing treatments to patients with high unmet needs.

A full summary is available via the Reagan-Udall Foundation website: https://reaganudall.org

ACADEMIC PERSPECTIVE (JM)

Disease background: MPS are heterogeneous, progressive disorders involving both physical and central nervous system (CNS) manifestations. Severe forms, MPS I, MPS II, MPS III, and MPS VII, are marked by cognitive decline, behavioural issues, and premature death.

CT challenges in neuronopathic MPS

- **Ultra-Rare population:** Fewer than 2,500 MPS patients in the U.S and only around 500 with severe forms (MPS I, II, IIIA), spanning a range of severity
- **Delayed onset:** While children typically develop normally for 1–2 years before regressing following a plateau, rate and duration of decline is variable between individuals
- **Irreversible damage**: At diagnosis, many already have substantial cognitive impairment. ERT in the brain post-symptom onset stabilises but does not reverse damage
- **Long trial duration needed**: A placebo-controlled trial with children under 3 would need to run 3–4 years to show significance, during which untreated children would suffer further irreversible decline
- **Placebo-controlled trials are unethical** in this context
- **Stabilisation is meaningful:** In progressive neurodegeneration, lack of further decline, even without improvement, can represent clinical benefit

CSF HS as a BM in MPS

CSF HS is reasonably likely to predict clinical benefit because:

- **More accurate than serum enzyme levels:** Lysosomal enzymes function only in acidic lysosomes, so elevated enzyme serum levels do not guarantee therapeutic effect
- **Reflects brain pathology:** CSF HS correlates with brain tissue levels and as CSF has a rapid turnover (4 times daily) it therefore reflects neuronal activity

Following the meeting, the FDA has allowed three companies to file BLAs under the accelerated approval pathway using CSF HS as a primary BM:

- Ultragenyx (UX111 for MPS IIIA): Priority review granted; decision expected August 2025
- Regenxbio (RGX-121 for Hunter syndrome): BLA submitted March 2025 using CSF D2S6 as the biomarker
- Denali Therapeutics (Tividenofsup alfa): BLA expected in early 2025 for Hunter syndrome

Facilitating accelerated approval

Peter Marks, Center for Biologics Evaluation and Research, FDA, USA

SUMMARY

- **Gene therapy is at a critical juncture** in rare diseases like MPS, facing **long timelines, complex regulations**, and **manufacturing hurdles** which often cause promising programs to be **abandoned**
- **When scientifically validated (as with CSF HS in MPS) BMs can accelerate development** by directly reflecting disease activity to enable earlier approvals and access to transformative treatments before irreversible damage occurs
- Advances in assay technology allow **precise, reproducible BM measurement**, supporting regulatory confidence and reducing the need for long-term trials
- The FDA supports this approach through initiatives like **START** and **CoGenT Global**, which **promote faster development** and **global regulatory alignment**

Gene therapy is at a critical juncture, particularly in rare diseases like MPS, where traditional development pathways are slow and costly. Long clinical timelines, global regulatory complexity, and manufacturing challenges often lead to programmes being abandoned, as seen in MPS, despite promising science. Recognising this, the FDA have increasingly leveraged the accelerated approval pathway to bring therapies to patients faster.

BMs are central, particularly in gene therapy development where they can help bridge the gap between known molecular targets and clinical benefit. While some BMs (e.g. factor activity in haemophilia) directly correlate with outcomes, others offer indirect but meaningful insights into disease activity and treatment effect. In MPS, HS is a valuable BM, not only because it reflects the underlying enzyme deficiency, but also because it is a toxic metabolite that contributes directly to disease pathology.

Measurement accuracy and precision are crucial. Modern technologies such as mass spectrometry and high-pressure liquid chromatography (HPLC) allow reproducible and reliable BM assessment, enabling confident use in long term clinical development. When BMs show robust, reproducible changes, using validated assays they can replace long-term clinical endpoints and support earlier approvals potentially saving years in drug development and allowing earlier access to patients before they suffer irreversible damage.

In gene therapy, randomized CTs are avoided where possible, particularly when large, reproducible changes in BMs can be demonstrated. In some cases, multiple BMs may be used to strengthen the evidence and support product development.

To support this, the FDA has launched pilot initiatives:

- START (Support for Clinical Trials Advancing Rare Disease Therapeutics): Focuses on enhanced, continuous communication to speed development particularly for high-need paediatric conditions
- CoGenT Global (Collaboration on Gene Therapies Global): aims to harmonize international regulatory requirements and enable coordinated reviews

The Center for Biologics Evaluation and Research, at the FDA is working to address challenges in the development of gene therapies, particularly for rare diseases, with the use

of BM as a key strategy. When scientifically validated, as in the case of HS in MPS, this approach can help accelerate access to life-changing treatments for affected children.

Biomarkers for MPS. The regulators' view (Committee for Medicinal Products for Human Use (CHMP)/ European Medicines Agency (EMA))

Emmely de Vries (E de V), Jan Span (JS), EMA / EU Network representatives

SUMMARY

- **Robust** evidence of **clinical benefit** is necessary for **benefit-risk assessment**
- **HS in the CSF, in the view of CHMP, cannot (yet) provide this robust evidence,** limited by the absence of defined thresholds and disease-stage related response variability. **Consistency across clinical outcomes** is more important than statistical significance on a single BM
- **RCTs remain necessary in MPS** to robustly assess treatment effect due to **disease heterogeneity**; clinical endpoints (e.g., cognition, adaptive behaviour) must be primary, with BMs as supportive
- Regulatory caution stems from past failures (e.g. Ocaliva) where BM-based approvals did not translate into clinical benefit; however, **totality of evidence** (e.g. Pegvaliase) can support approval
- **Early scientific engagement** is strongly encouraged through national or EMA advice, and the **PRIME scheme** is available for **promising therapies in high unmet need areas**

The CHMP is the EMA's committee responsible for human medicines. The presentation gave the CHMP perspective.

Types of Marketing Authorizations in the EU

- **Full marketing authorisation (FMA):** Granted when the data package is comprehensive, and the benefit risk balance is clearly positive
- **Conditional marketing authorisation (CMA**): Granted with incomplete data where there is unmet need and the immediate availability of the product outweighs the risk to the public, provided the applicant can supply full data within a reasonable timeframe
- **Marketing authorisation under exceptional circumstances (MAUEC):** Used when full data cannot be obtained due to rarity of the disease or ethical constraints on CTs

Benefit/risk (B/R) assessments are the basis for CHMP decision making – do the benefits of a drug outweigh its risks?

A variety of factors are considered in the B/R assessment including:

- **Burden of disease:** Higher risk may be acceptable for serious conditions like MPS
- **Type of treatment:** Curative vs symptomatic treatment

- **Scope of treatment effect:** Full or partial symptom coverage (e.g. peripheral vs CNS)
- **Clinical relevance:** Of both the treatment effects and safety profile
- **Unmet need:** Assessed in context of available treatment options

A measurable clinical benefit is essential for a positive B/R assessment. Current CHMP viewpoint on the B/R assessment:

- The CHMP bases B/R assessments on the consistency of effects across clinical endpoints, which is especially critical in rare disease where large powered studies may not be feasible
- Consistent clinical benefit across multiple endpoints carries more weight than statistical significance on a single BM
- As noted by E. de Vries, statistical significance is less important than clinical relevance when consistency across clinical outcomes is demonstrated

Both CMA and MAUEC require a positive B/R and carry post-authorisation obligations, such as safety or efficacy studies (e.g. registry studies), and routine pharmacovigilance. CMA may be converted to FMA once obligations are fulfilled.

BM use

It is important to consider the different types of BMs and the purpose they serve. Pharmacodynamic or response BMs provide confirmation of the mechanism of action and supportive evidence of efficacy, e.g. decreased enzyme substrate in ERT. These are distinct from BMs for disease status e.g. decreased NfL (a BM not validated as a surrogate for efficacy but reflects neurological damage).

From a regulatory perspective, true surrogacy is a very high hurdle: a valid surrogate must not only be affected by the intervention but must also directly mediate the effect on the clinical outcome. In contrast, several scenarios undermine surrogacy [Fleming TR 1996;25:605-13]:

a) A disease has an impact on the surrogate, but the disease and outcome are linked by different mechanisms
b) The surrogate only partially influences the outcome while other disease pathways remain active
c) The intervention impacts the clinical outcome regardless of the surrogate
d) All three of these factors are present

In MPS no BM, including CSF HS, has been validated as a true surrogate endpoint**,** meaning a between-group difference in HS levels cannot reliably be translated into measurable clinical benefit. Key challenges include:

- Unclear sensitivity to change of current BMs
- No defined minimal clinically important difference (MCID), making it uncertain what effect size is clinically meaningful

As shown in the data presented in this meeting, HS reduction does not consistently predict clinical benefit. For example, normalising HS in early-stage disease may correlate with

cognitive improvement, while the same reduction in a patient with advanced neuronal damage may yield no measurable gain.

CHMP remains cautious about relying solely on BMs due to past cases where they failed to demonstrate clinical benefit:

Example 1: The Ocaliva Case
Ocaliva, was approved for primary biliary cholangitis under CMA based on liver function BMs. However a required post-marketing RCT showed no clinical benefit, leading to withdrawal of the CMA in the EU due to an unfavourable benefit/risk profile.
Example 2: Pegvaliase – Phenylketonuria (PKU)
Assessed using a pharmacodynamic primary endpoint, reduction of blood phenylalanine (Phe), based on an 8-week randomised withdrawal phase. While the BM showed statistically significant changes, this alone was not sufficient to confirm clinical benefit, particularly due to the lack of consensus on adult treatment targets. However, the totality of evidence, including secondary endpoints showing trends toward neurocognitive improvement and increased protein tolerance, supported a positive CHMP opinion.

Current CHMP viewpoint on the study design

- RCTs are necessary to robustly estimate treatment effect especially in a heterogenous disease like MPS where disease stage significantly influences cognitive outcomes
- A clinical primary endpoint is required, which likely necessitates at least 2 years of follow-up to draw meaningful conclusions on cognitive and adaptive behavioural endpoints
- BMs should be co-primary or important secondary endpoint (study powered on it) to confirm MoA and PD effect

Biomarkers as clinical endpoints in the context of rare disease: an MHRA perspective

Shirley Hopper (SH), MHRA, UK

SUMMARY

- The **MHRA** offers **flexible regulatory pathways for rare diseases**, including **conditional** and **exceptional circumstances authorisations,** and **orphan drug incentives** (e.g. 10 years of market protection, fee reductions)
- **Validated biomarkers may be accepted as surrogate endpoints if strongly predictive of clinical benefit;** less-validated BMs may be considered under conditional approval or EAMS on a case-by-case basis, but a **positive B/R must be demonstrated**
  - BM **assay validation is key**
  - **UK CT authorisation does not imply validation of a surrogate endpoint**

- New MHRA guidance (Q1/Q2 2025) will support use of **historical and real-world data as external controls**, which may be well suited for MPS trials
- Developers are encouraged to **engage early** with MHRA, including through the **Innovative Licensing and Access Pathway (ILAP),** to accelerate access

The MHRA is the UK regulator for medicines and medical devices, ensuring they meet safety, quality, and efficacy standards. In this context, its key role is supporting early access to safe, effective treatments through national and international collaboration.

UK medicines regulatory framework for rare disease

While full marketing authorisation (FMA) requires comprehensive data with minimal uncertainty other types of authorisation pathways are available within the UKs regulatory framework for rare disease with post authorisation obligations to address remaining uncertainties are addressed.

Benefit/risk assessments of clinically meaningful endpoints are central to decision making:

To grant marketing authorisation, the MHRA must see clear therapeutic benefit outweighing risks. Assessments consider disease burden, scope of treatment effects (e.g., CNS vs peripheral effects), relevance of outcomes to families, safety profile, and the availability of alternative therapies.

Traditionally evidenced using pivotal trials with primary endpoints that are clinically meaningful such as survival, symptom improvement, or disability progression. **In serious conditions such as MPS, higher risk may be acceptable but measurable clinical benefit, and a positive B/R assessment must be demonstrated.**

- **Conditional marketing authorisation:** Available when comprehensive clinical data not yet available in cases of seriously debilitating of life-threatening diseases with unmet need
- **Marketing authorisation under exceptional circumstances:** For example, when a comprehensive data package cannot be provided e.g. because the condition is very rare

Other provisions include:

- **Orphan medicines provisions:** Granted at marketing authorisation, offering 10 years of market protection (plus 2 for paediatric indications) and licensing fee reductions to support rare disease drug development
- **The MHRA Early Access to Medicines Scheme (EAMS)** (free of charge scheme): *"Aims to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need"*

BMs as endpoints

Validated BMs can replace clinical outcomes to shorten trials, but only if strong evidence shows they reliably predict clinical benefit. This requires data from trials demonstrating

effects on both the BM and clinical endpoint. New validation is needed for each disease and intervention type due to the risk of off-target effects.

In serious conditions with high unmet need, less-validated surrogates may be accepted on a case-by-case basis under conditional authorisation routes or the EMAS. As with the EMA, caution is advised for BM surrogates with a natural history correlation only that may not be directly linked to the causal disease pathway.

Assay validation in line with Good clinical practice (GCP) principles is essential to ensure reliable data for regulatory decision making. This is especially critical in rare diseases, where limited data heightens the need for accuracy and validity (as per EMA guidance).

Guidance on trials and regulatory support in rare diseases

- **CT review:** The MHRA, in line with regulations, ensures participant safety, scientific validity, and a favourable benefit/risk for study participants. However, MHRA trial approval does not imply endorsement of a surrogate endpoint or confirm suitability for licensing decisions
- **Placebo-controlled studies in rare diseases:** The MHRA are finalising guidance on the use of historical controls of real-world evidence which will be published Q1/Q2 2025. MPS would be a classic setting where external controls may be more appropriate
- **Early regulatory engagement is encouraged.** Developers can seek scientific and regulatory advice at various stages, including trial authorisation, marketing authorisation, and the use of surrogate endpoints
    - **The Innovative Licensing and Access Pathway (ILAP),** recently re-launched, is open to both commercial and non-commercial sponsors and supports faster access to transformative medicines. It enables collaboration with MHRA, Health Technology Assessment (HTA) bodies (e.g. National Institute for Health and Care excellence (NICE), Scottish Medicines Consortium (SMC)), and the broader UK healthcare system

Panel discussion

(Emmely de Vries (E de V), Jan Span (JS), Joseph Muenzer (JM), Susan Winckler (SW), Shirley Hopper (SH))

SUMMARY: PANEL DISCUSSION – VIEWS FROM THE REGULATORS

- **Placebo-controlled trials** in **MPS** are **ethically and practically challenging** due to **rapid neurodegeneration** and **small patient populations**. Regulators acknowledged that **consistent trends** toward **stabilisation and deviation from natural history** may be **clinically meaningful** and support **alternative trial designs** or **approval under exceptional circumstances**
- **HS shows promise as a BM reasonably likely to predict benefit**, especially for accelerated or conditional approval. Regulators emphasised that while **not yet** a **validated surrogate**, totality of data is crucial and HS reduction supported by short term trends evidencing **clinical benefit** on multiple meaningful endpoints could enable **earlier access,** with **confirmatory follow-up**

- **Regulators are open to flexibility in BM use, trial design, and lab compliance,** particularly in **rare diseases with high unmet need.** Early developer engagement and collaborative data sharing were strongly encouraged to expedite patient access

1. **Are placebo-controlled trials feasible or ethical in ultra-rare, progressive diseases like MPS, particularly when long-term follow-up (4–5 years) is needed to detect meaningful clinical change?**

   SH (MHRA): In certain cases, external controls may be appropriate, especially when natural history shows a particular clinical outcome is unattainable without treatment. While two years is often insufficient for statistical significance on a clinical endpoint, consistent trends toward stabilisation rather than improvement can still be clinically meaningful.

   JS (EMA): EMA has seen cases where reliance on surrogate endpoints alone has led to unsuccessful outcomes. In MPS, while multiple BMs exist, improvements in daily functioning, communication, and cognition are key. Marketing under exceptional circumstances may be considered, with annual reviews to monitor stability and meet agreed conditions. Over time (e.g. 5–10 years), stability or improvement in cognition can support continued authorisation.

   JM: Raised ethical concerns about placebo-controlled trials exceeding two years in progressive diseases like MPS, highlighting the potential harm to control group participants.

   JS (EMA): Agreed, stating that in his personal view, such long-term placebo use is unethical. Meaningful changes in cognition, speech, and daily life activities can often be observed within 1–2 years. While no validated BMs exist for these functional domains, tools like the Bayley Scale can capture treatment effects. Companies should engage early with EMA to define conditions for potential approval, rather than delaying access for 2–10 years. Evidence showing deviation from natural history toward normal development is considered valuable at any stage. However, for BMs to support approval, randomised comparison is still needed, at least short-term (e.g. 6 months), to show superiority over placebo on pharmacodynamic endpoints. Crucially, BM changes must be correlated with clinical outcomes to be meaningful for regulators.

   PM (FDA): Highlighted the ethical dilemma in rare diseases: whether to withhold a potentially beneficial treatment or provide access to one that might not work. In these cases, the FDA supports using a BM to make an informed early decision, followed by longer-term data collection. Over time, it becomes clear whether patients deviate from the natural history trajectory, indicating effectiveness even without a randomized controlled trial.

   In gene therapy, where effects are expected to be substantial, this approach is more justifiable. MPS is seen as a strong example, with a totality of evidence compared to other disease areas, epitomised in Dr. Muenzer's rationale for CSF HS as a BM, that could support accelerated approval. Hypothetically, a one-year trial showing HS normalization could justify early approval, followed by 3–5 years of confirmatory follow-up. The potential benefit of this approach is preventing 2–4 years of decline. The risk is

some uncertainty, but patients would still have received the best available option at the time – 'the perfect is the enemy of the good'.

The concern in the U.S. is that patients may gain access to treatments without structured data collection, which could undermine both evidence generation and regulatory oversight, creating a worse scenario than controlled, monitored access.

SW: Added that global regulatory frameworks vary, with the U.S. moving toward broader access to investigational products, which shifts the regulatory landscape and requires consideration

2. **Given the early irreversible neurodegeneration in MPS, how can we foster an environment that generates robust clinical data to support regulatory confidence, and are there examples of surrogate BM use?**

   SH (MHRA): BMs have been used to support conditional approvals, for example, biochemical endpoints in primary biliary cirrhosis and tumour response in oncology (not a validated surrogate endpoint).

   Though no formal MHRA position on MPS was given, she noted the evidence presented today is strong and may be enough to support conditional marketing authorisation based on CSF HS, with post-approval confirmatory data. She encouraged developers to engage early and present their data.

3. **Given the global nature of rare disease trials and the difficulty in finding compliant laboratories, what are the regulators perspectives on the use of non-compliant labs for BM assays in rare disease trials?**

   PM (FDA): If a programme begins with the use of assays in a non-compliant lab, it may be treated as a research assay. If reasonably accurate and precise, it can be used early in development, with a plan to transition to a validated, compliant assay. The FDA supports co-development, allowing assay validation to progress in parallel with the trial, particularly in rare diseases where the cost of full diagnostic validation may exceed the market for these products.

   SH (MHRA): Agreed, adding that MHRA would work with developers to preserve and re-test samples centrally, even post-approval. However, if the assay supports a primary endpoint, higher assurance is needed, though development should not be stalled over assay cost.

   JS (EMA): Concurred, noting the regulatory approach depends on whether the BM is used as an exploratory or primary endpoint.

4. **What would be the proposed alternative to BMs and conditional approval particularly in the case of Sanfillipo as there is a lot of heterogeneity and the standard trial would take more than 5 years?**

   E de V (EMA): It is encouraging that some companies have compiled full datasets, suggesting it's possible with standard procedures even in rare conditions. For BM to support conditional approval, data must align with established criteria for surrogate endpoints. She emphasized the need for a collaborative approach, urging companies and academia to pool data and make a collective case. A unified dataset could strengthen regulatory assessment and accelerate access.

JS (EMA): Advice within national frameworks can be more flexible than within international regulatory frameworks

E de V (EMA): Had personally hoped to see more data to evidence the use of HS as a BM. While acknowledging that 5-year placebo-controlled trials may be unethical, is equally unethical to prescribe treatments without clear evidence of efficacy, especially when risks are involved.

PART 5 – SUMMARY AND FINAL THOUGHTS

KEY MESSAGES: PART 5 – SUMMARY AND FINAL THOUGHTS

- HS drives neurodegeneration in MPS, and while reducing HS is essential, early treatment before irreversible damage is critical for meaningful clinical outcomes. Stabilisation in advanced cases still offers clinical value
- Newborn screening cannot be implemented without an approved treatment, yet demonstrating the full benefit of treatment requires identifying patients before symptoms appear, which screening would enable
- HS is a sensitive early BM that reflects disease activity and can be used to demonstrate early treatment effect, enabling shorter, more feasible trials and supporting accelerated approval pathways
- RCTs in MPS are often unfeasible or unethical due to rapid disease progression and small patient populations
- There is an urgent need for regulatory flexibility and support for BM-based approvals to enable earlier access to life saving treatments

Panel discussion

(Cara O'Neill (CO'N), Joseph Muenzer (JM), Simon Jones (SJ), Matthew Ellinwood (ME))

1. **Why HS is an appropriate BM for MPS? Are there situations where HS levels are reduced with no clinical response?**

   ME: Emphasised that HS accumulation clearly drives neurodegeneration in MPS. While reducing HS is key, outcomes depend heavily on timing, early treatment, before irreversible damage, is critical (e.g. before age 2–3 years in MPS I). In advanced cases, stabilisation is meaningful. Newborn screening requires an approved treatment yet, we cannot recruit pre-symptomatic patients to demonstrate optimal treatment efficacy without screening.

2. **How quickly can we observe improvements in BM after treatment and what type of time frame should be communicated about clinical benefit?**

   JM: In CTs for MPS I and MPS II CTs, clinicians could tell on examination which patients received treatment within 2/3 weeks and dramatic BM reductions were seen within 4–8 weeks. However, clinical benefit depends on baseline severity and timing of treatment. Placebo-controlled trials are sacrificing a whole generation.

3. **How should we treat patients where treatment is not able to reverse the damage that has already occurred but can improve QOL?**

   CO'N: QoL is often viewed as less than other measures but is actually composed of measurable clinical endpoints like mobility, oral intake, and whether a gastrostomy tube is needed. Outcomes that are appropriate even when improvement is not possible must considered. All children deserve treatment, even if reversal isn't possible.

JM: The totality of data matters; everything needs to be captured and evaluated.

SJ: While CSF HS reduction may not always match clear clinical improvement in advanced stages, some clinical benefit is almost always present—the challenge is how to measure it meaningfully.

4. **How do we ethically manage randomised studies in MPS?**

   SJ: Everyone wants well designed robust studies, ideally double blind RCTs but these are not always ethical or feasible in rare, progressive diseases. Accelerated approval using BMs with long term follow up is the best alternative. Attempting to force these diseases into rigid 12–24-month trial models has often failed to the detriment of patients and their families. Open dialogue with the MPS community is needed to define what's ethical on a case-by-case basis.

5. **Final reflections from the patient community?**

   CO'N: Regulatory systems must be flexible to accommodate challenges in rare disease and allow for disease-specific timelines, which often do not align with traditional approval models. This discourages sponsors from entering the space. While families may not focus on company success, they do care about access to trials and treatments and that requires financial sustainability for sponsors. Patients and families are part of the ecosystem and must be included in the conversation.

Closing remarks

Kim Angel – Executive Director, International MPS Network (IMPSN)

KA closed the meeting by emphasizing the urgency of accelerating access to treatments for children with MPS. While no regulatory changes have been achieved today, the active engagement of agencies such as the EMA and MHRA in these conversations is an encouraging first step towards more responsive regulatory pathways for future therapies.

A key theme throughout the meeting was **time**; children with MPS do not have **time**, and parents are desperate for more. The emotional toll on families and the impact of regulatory delays were made clear, as many trials have been halted despite promising data.

She highlighted the shift underway in the U.S. regulatory approach and expressed hope for similar progress globally. MPS knows no borders, and with regulators now open to scientific dialogue, there is optimism that data can be used to accelerate access to life-changing treatments.

REFERENCES

Argueta C, *et al.* A link between baseline neurofilament light chain and primary substrate accumulation in cerebrospinal fluid, and clinical outcomes in patients with MPS II from a phase 2/3 clinical trial and extension study of intrathecal idursulfase. *Mol Genet Metab* 2025;144(3):109055.

Austin *et al* in preparation,

Brennan T, *et al.* Heparan sulfate, an endogenous TLR4 agonist, promotes acute GVHD after allogeneic stem cell transplantation. *Blood* 2012;120:2899-2908.

Dekaban AS, Constantopoulos G. Mucopolysaccharidoses. Relation of elevated cerebral spinal fluid to mental retardation. *Arch Neurol* 1973;28(6):385-8.

Dickson PI, *et al.* Specific antibody titer alters the effectiveness of intrathecal ERT therapy in canine mucopolysaccharidosis I. *Mol Genet Metab* 2012; 106(1):68-72.

Dierenfeld AD, *et al.* Replacing the enzyme alpha-L-iduronidase at birth ameliorates symptoms in the brain and periphery of dogs with mucopolysaccharidosis type I. *Sci Transl Med* 2010;2(60):60ra89.

Ellinwood NM, *et al* Tralesinidase Alfa Enzyme Replacement Therapy Prevents Disease Manifestations in a Canine Model of Mucopolysaccharidosis Type IIIB. *J Pharmacol Exp Ther* 2022;38(3):277-286.

Fleming TR, *et al.* Surrogate end points in clinical trials: are we being misled? *Ann Intern Med* 1996;25:605-13.

Fumagalli F, et al. Long-Term Effects of Atidarsagene Autotemcel for Metachromatic Leukodystrophy. *N Engl J Med.* 2025; 392(16):1609-20.

Ghosh A, *et al* High dose genistein in Sanfilippo syndrome: A randomised controlled trial. *J Inherit Metab Dis* 2021;44(5):1248-1262.

Ginsberg SD, *et al* Accumulation of intracellular amyloid-beta peptide (A beta 1-40) in mucopolysaccharidosis brains. *J Neuropathol Exp Neurol* 1999;58(9):815-24.

Jones S, *et al.* A phase 1/2 study of intrathecal heparan-N-sulfatase in patients with mucopolysaccharidosis IIIA. *Mol Genet Metab* 2016;118(3):198-205.

Kakkis E. Mol Genet Metab. The transformation of drug development for the 21st century: Time for a change. 2022;137:107-113.

Lavery C, *et al.* Mortality in patients with Sanfilippo syndrome. *Orphanet J Rare Diseases* 2017;12(1):168.

Martins C, *et al.* Neuroinflammation, mitochondrial defects and neurodegeneration in mucopolysaccharidosis III type C mouse model. *Brain* 2015; 130:336-355.

Mikulka CR, *et al.* Cell-autonomous expression of the acid hydrolase galactocerebrosidase. *Proc Natl Acad Sci* U S A 2020 117(16):9032-9041.

Muschol N, *et al.* A phase I/II study on intracerebroventricular tralesinidase alfa in patients with Sanfilippo syndrome type B. *J Clin Invest* 2023;133(2):e165076.

Okur I, et al. Longitudinal natural history of pediatric subjects affected with mucopolysaccharidosis IIIB. *J Pediatr* 2022;249:50-8.

Parish CR. Heparan sulfate and inflammation. Nature Immunol 2005;6(9):861-2.

Pica N, *et al.* Discontinuation and nonpublication of randomized clinical trials conducted in children. *Pediatrics* 2016;138(3):e20160223.

Raegan Udall Foundation. Qualifying BMs to support rare disease regulatory pathways https://reaganudall.org/news-and-events/events/qualifying-biomarkers-support-rare-disease-regulatory-pathways. Accessed on 27/03/2025.

Sandwall E, *et al.* Heparan sulfate mediates amyloid-beta internalization and cytotoxicity. *Glycobiology* 2010:20(5):533-541.

Shapiro EG, *et al*. A Prospective Natural History Study of Mucopolysaccharidosis Type IIIA. *J Pediatr* 2016;170:278-87.e1-4.

Snow AD, *et al.* Early accumulation of heparan sulfate in neurons and in the beta-amyloid protein-containing lesions of Alzheimer's disease and Down's syndrome. *Am J Pathology* 1990;137(5):1253-70.

Speich B, *et al*. Nonregistration, discontinuation, and nonpublication of randomized trials: A repeated metaresearch analysis. *PLOS Med* 2024;19(4): e1003980.

Terry K, Linker A. Distinction among four forms of Hurler's syndrome. *Proc Soc Exp Biol Med* 1964;115:394-402.

Vera MU, *et al*. Evaluation of non-reducing end pathologic glycosaminoglycan detection method for monitoring therapeutic response to ERT in human mucopolysaccharidosis I. *Mol Genet Metab* 2020;129(2):91-97.

Whiteman DA, *et al.* Development of idursulfase therapy for mucopolysaccharidosis type II (Hunter syndrome): the past, the present and the future. *Drug Des Devel Ther* 2017;11:2467-2480.

Wijburg FA, *et al.* An observational, prospective, multicenter, natural history study of patients with mucopolysaccharidosis type IIIA. *Mol Genet Metab* 2022;135(2):133-142.

Wijburg presented at ACMG 2013.

Zalla C *et al.* Glial degeneration with oxidative damage drives neuronal demise in MPSII disease. *Cell Death and Disease* 2016;7:e2331.

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For further information, please contact:

The MPS Society
Website: www.mpssociety.org.uk
Email: mps@mpssociety.org.uk

The International MPS Network (IMPSN)
Website: www.impsn.org
Email: info@impsn.org

Rare Disease Research Partners

Rare Disease Research Partners
MPS House, Repton Place, White Lion Road
Amersham, Buckinghamshire, HP7 9LP, UK
t: +44 (0) 345 260 1087
e: info@rd-rp.com

w: rd-rp.com