

Two Generations of Mitochondrial Augmentation Technology: Clinical Advances in Treating Primary Mitochondrial Disease

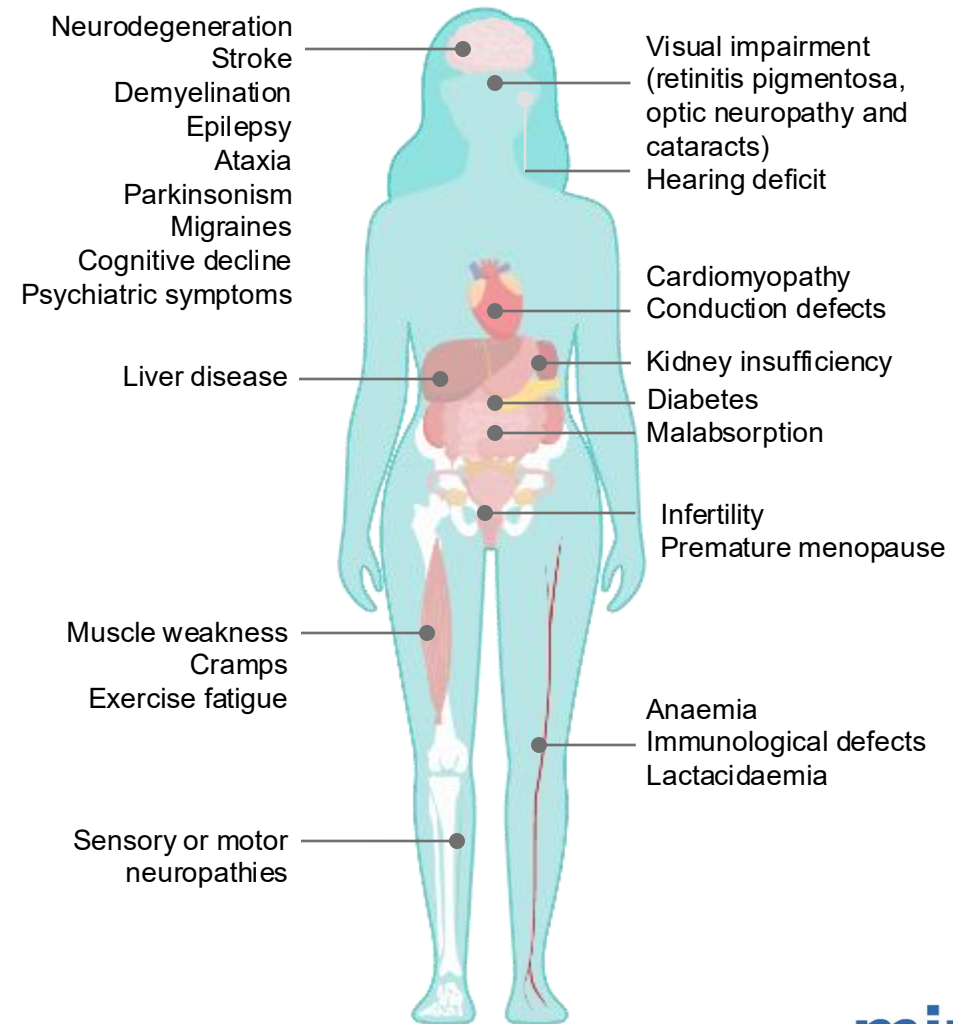
Dr Noa Sher, Chief Scientific Officer, Minovia Therapeutics



How can we target multi-systemic disease?

Mitochondrial diseases are complex and affect multiple organ systems

The bloodstream circulates between all the organs and may achieve multi-organ improvement



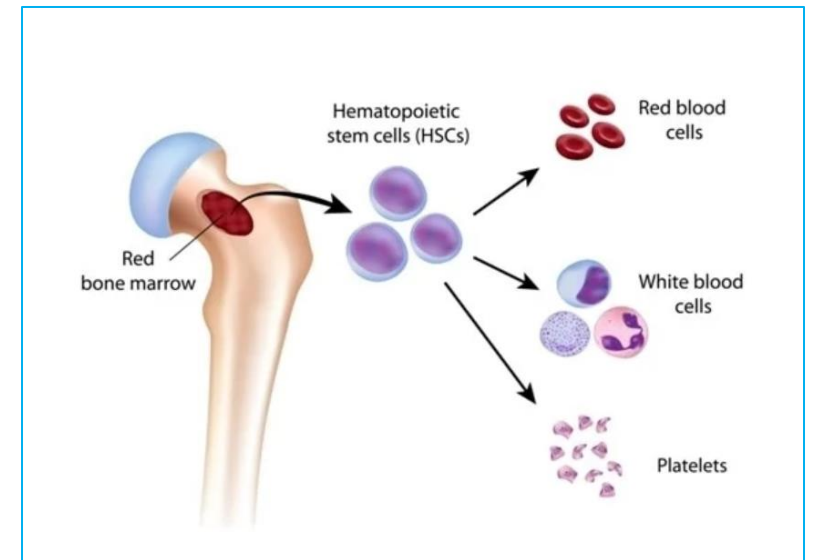
Why Human Hematopoietic Stem and Progenitor Cells?

Dysfunctional mitochondria in immune cells induce multi-organ morbidity

Healthy and Functional Mitochondria are Required for Normal Hematopoiesis

Mitochondrial dysfunction in HSPCs results in:

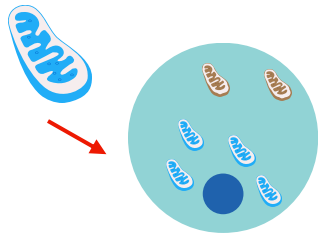
- Reduced ability to differentiate to mature cell types
- Immune system dysfunction
- **Impaired function of additional organs** (muscular, cognitive, cardiovascular), by mechanisms not fully understood



Mitochondrial function in the hematopoietic system is critical for blood and immune system function, but also for functionality of multiple organ systems

Mitochondrial Augmentation Technology (MAT)

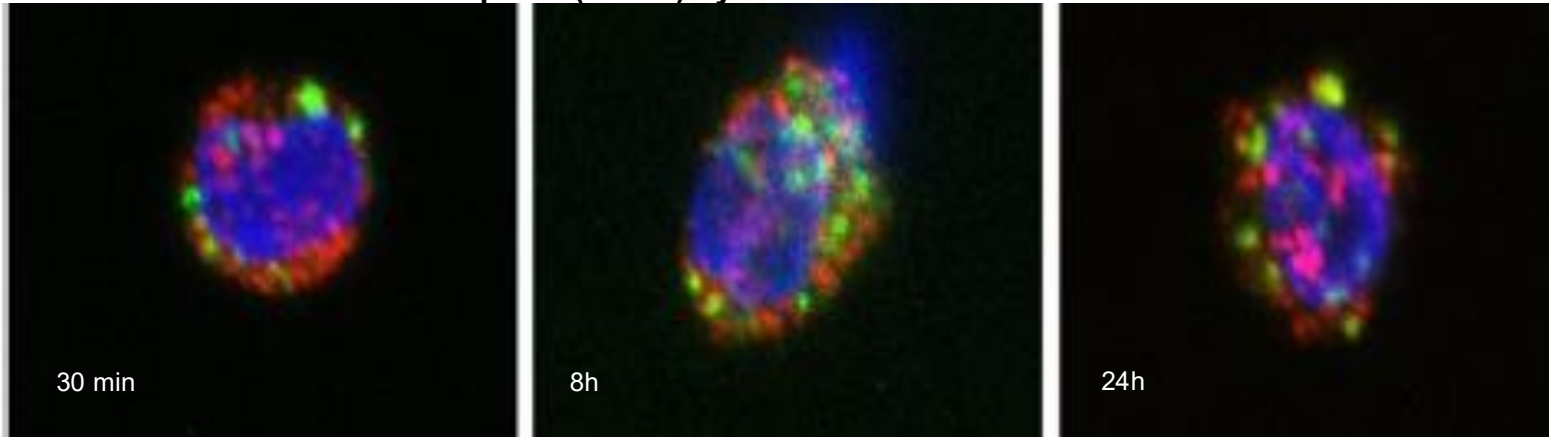
Scientific breakthroughs in understanding the ability for isolated mitochondria to transfer into human cells form the foundation MAT



Mitochondria can enter cells, rebuild normal mtDNA content in recipient cells under specific conditions, restore functionality and transfer between cells

Minovia Invented a Process of Mitochondrial Transfer into Human Cells

Time Course of Mitochondria Uptake (Green) by Human HSPCs

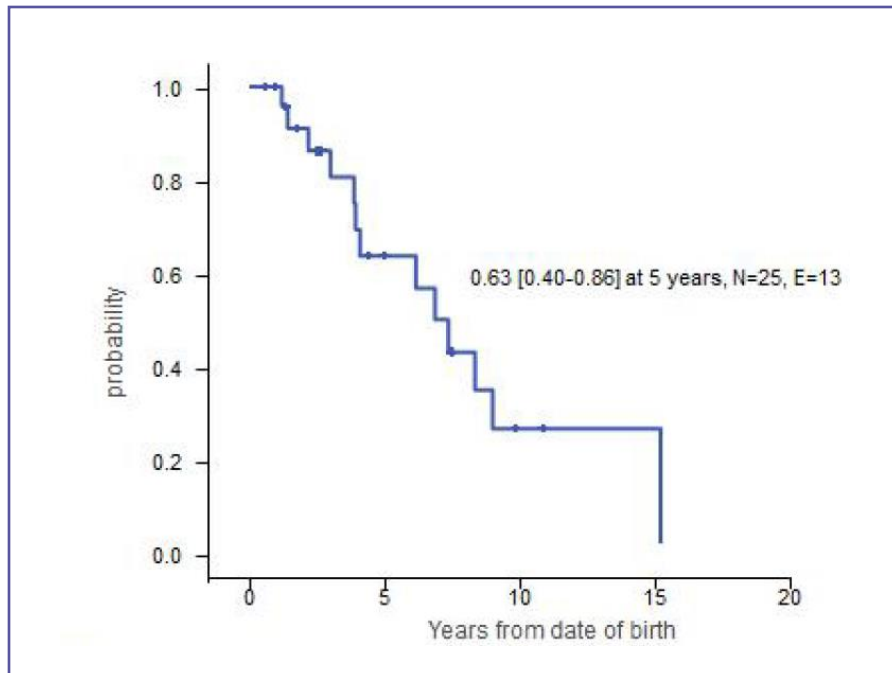


GFP-Mitochondria: HeLa Cells, Recipient Cell: Human CD34+
Jacoby *Nat Regen Med* 2021

Mitochondrial Dysfunction in Bone Marrow Failure: Pearson's Syndrome: a Mitochondrial Deletion Syndrome

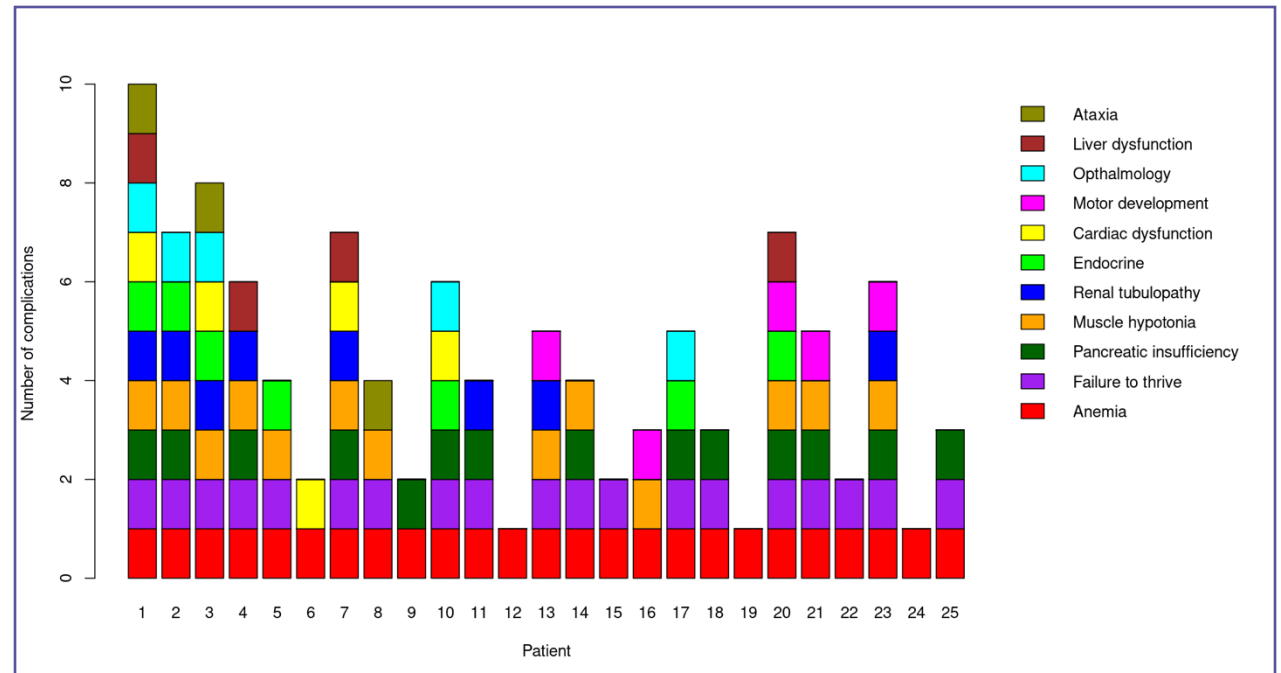
Pearson's Syndrome involves large-scale mtDNA deletions (in multiple organs) resulting in a severe, multi-systemic, fatal pediatric disease

Pearson's Syndrome Survival Curve



Adapted from Yoshimi *Brit J Haematol* 2021

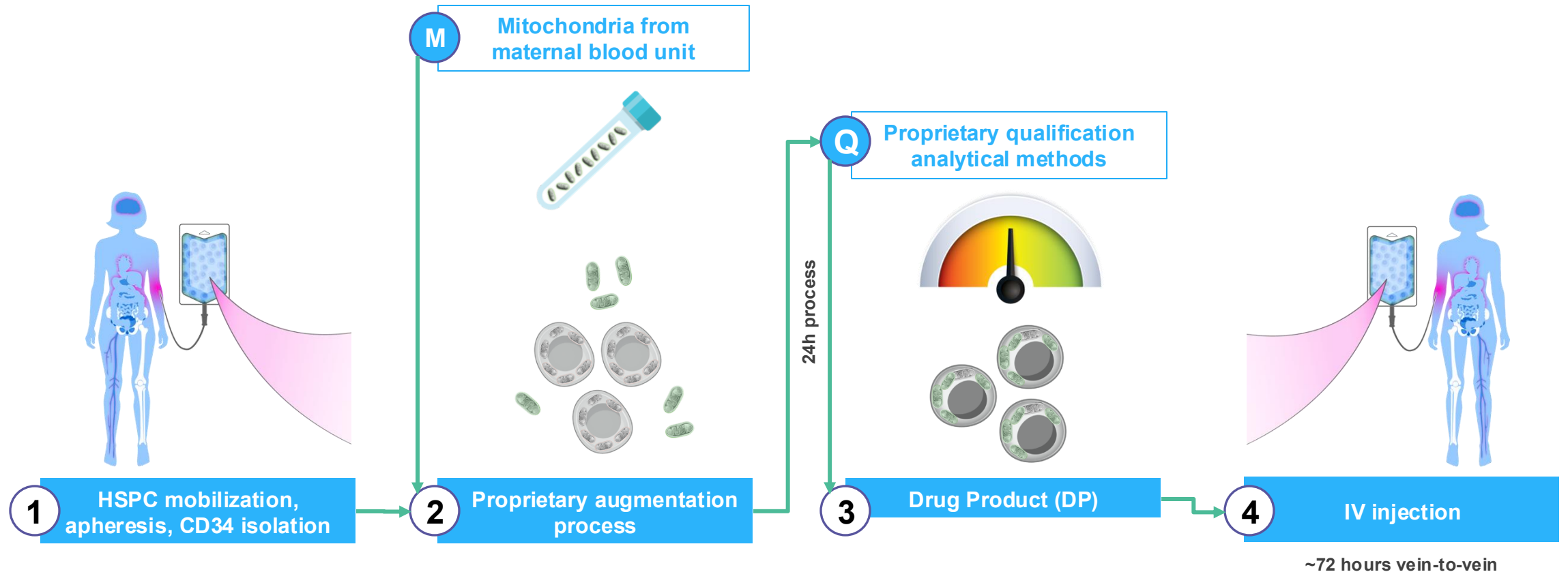
Pearson's Syndrome Multi-Systemic Phenotype



Adapted from Yoshimi *Brit J Haematol* 2021

Mitochondrial dysfunction leads to anemia and dysfunction of multiple organ systems

1st Gen Product: Autologous HSPC Enriched with Maternally Derived Mitochondria



**Guiding principle: First, do no harm.
No conditioning. Syngeneic. Ex vivo.**

Treated total of 12 PMD patients with MNV-101

Compassionate Use Was Provided To Pearson Syndrome and Kearns Sayre Syndrome Patients

Challenges of understanding outcomes in heterogeneous population

- Challenging to objectively assess outcomes in heterogeneous population
 - Age (2-17)
 - Presenting symptoms
 - mtDNA deletion size and location (2-8 kb)
 - mtDNA heteroplasmy level (4-70%)
- Compassionate use studies enabled better assessment of where we can provide the most benefit, and what changes we can expect to see, setting the stage for selection of clinical trial outcome measures

Table 1. Baseline clinical characteristics of patients with mtDNA deletions treated with MAT. +, symptomatic functional failure; ++, functional failure requiring medical interventions (such as transfusion, gastrostomy-based feeding, dialysis, and pacemaker). MAT, mitochondrial augmentation therapy; PS, Pearson syndrome; KSS, Kearns-Sayre syndrome; NA, not available.

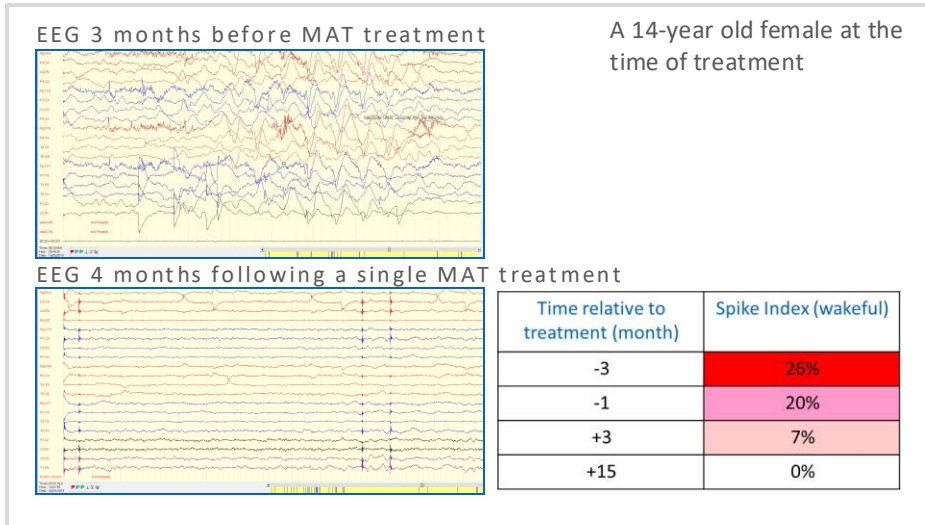
Patient	1	2	3	4	6	7
Primary mitochondrial disease	PS	PS	PS	KSS	KSS	PS
Gender	Male	Female	Female	Female	Male	Female
mtDNA deletion	3.9 kb (5835–9753)	2.3 kb (12,113–14,421)	4.97 kb (8470–13,447)	7.4 kb (7194–14,959)	4.97 kb (8470–13,447)	6.7 kb (9102–15,815)
Age at diagnosis	15 months	NA	14 months	9 years	3.5 years	12 months
Presenting symptoms	Pancytopenia, recurrent febrile episodes	Transfusion-dependent anemia, failure to thrive, diabetes mellitus, renal tubulopathy	Recurrent pneumonia, transfusion-dependent anemia	Recurrent nocturnal vomiting, strabismus with vision deterioration	Failure to thrive, diarrhea	Thrombocytopenia, renal tubulopathy, lactic acidosis
Age at MAT (years)	6.5	10.5	7	14	17	2
Baseline heteroplasmy in peripheral blood (%)	70	4	18	46	8	69
Organ involvement at baseline						
Hematologic*						+
Neurologic	+	++		++	++	+
Poor feeding	++	++	+	++		+
Endocrinopathy						
Diabetes		++	++			++
Parathyroid	++		+	+	++	++
Other†				+	++	++
Renal						
Renal failure	+	++			+	
Tubulopathy	++		+	++	++	++
Liver transaminitis		+				
Ophthalmic		+	+	+	+	
Cardiac conduction	+	+		+	++	

*At baseline evaluation before MAT; a history of transfusion-dependent anemia was present in additional patients. †Included adrenal insufficiency (n = 2), delayed puberty (n = 2), and hypothyroidism (n = 1).

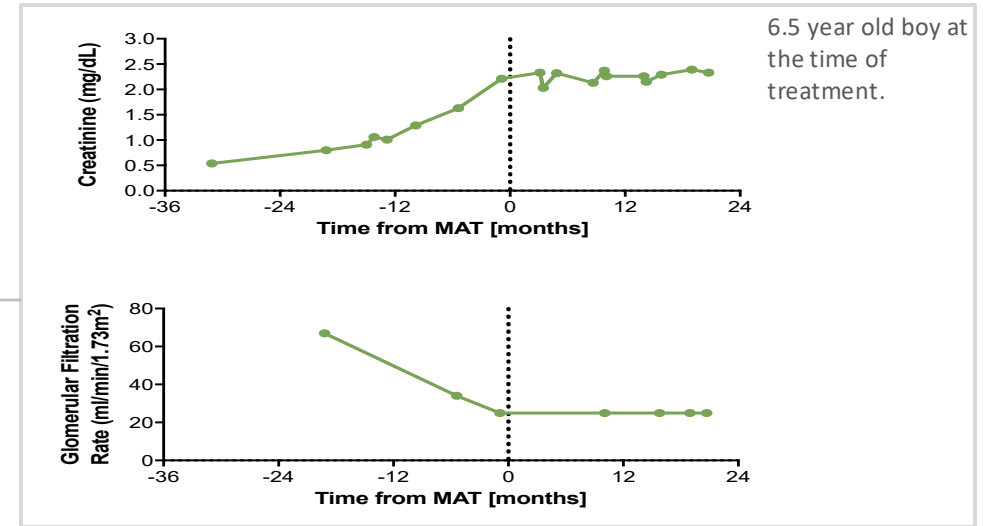
Clinical Proof of Concept: First Generation Product (MNV-101)

Demonstrated significant improvement in growth and multiple organ systems

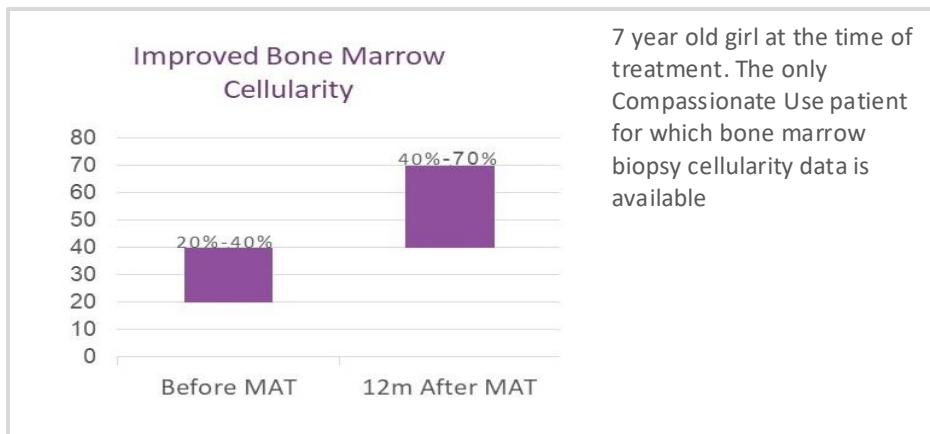
Reduction of epileptic activity post-MAT in a KSS patient



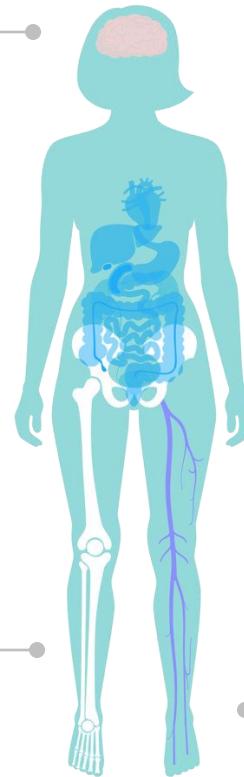
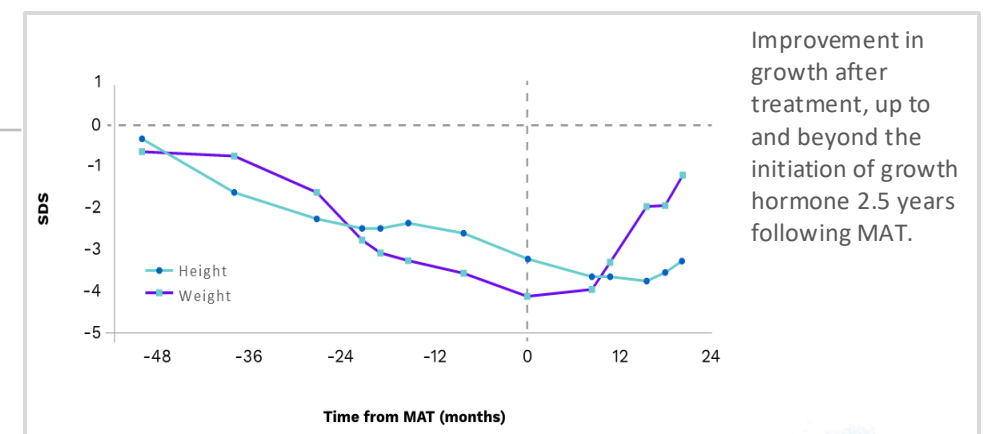
Renal function stabilized post-MAT in a PS patient



Increase in BM cellularity post-MAT in a PS patient



Improvement in Growth post-MAT in a PS patient



Pediatric patients with Primary Mitochondrial Diseases (PMD)

Pearson Syndrome Clinical Trial of MNV-101

First generation syngeneic/maternal derived product (MNV-101) demonstrated efficacy in primary genetic mitochondrial diseases, providing proof of concept for MAT.

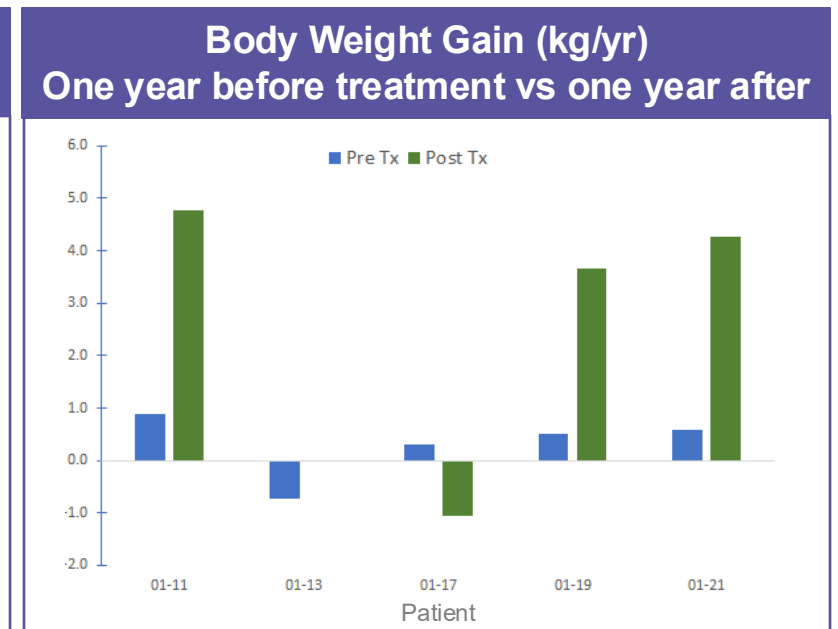
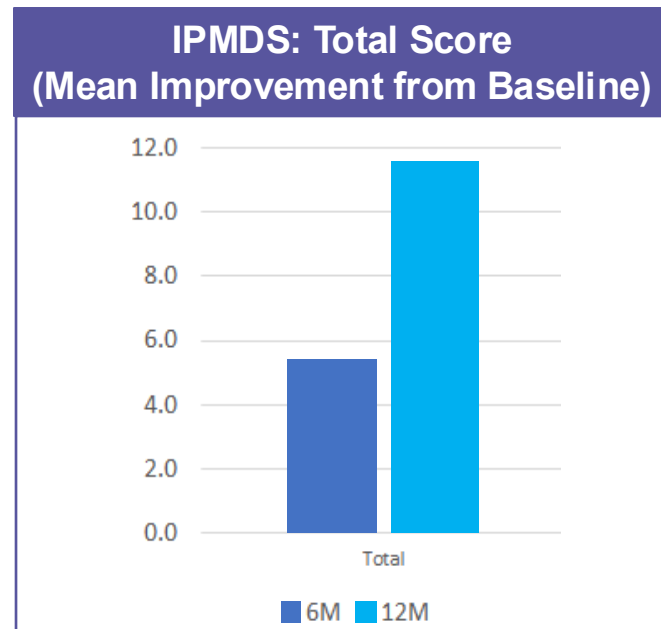
MNV-101 Clinical Data:

Compassionate use open-label treatment

- **7 patients:** 4 Pearson's Syndrome, 2 Kearns-Sayre Syndrome, 1 Leigh Syndrome
- 3 to >6 years follow-up post treatment

Phase 2 Clinical Study in Pearson's Syndrome

- **5 Pearson's Syndrome patients**
- **Primary endpoint:** International Pediatric Mitochondrial Disease Scale (IPMDS)
- **Secondary endpoint:** body weight gain one year before treatment vs one year after



Additional areas of improvement across patients:

- Neurocognitive function
- Muscle function
- Coordination
- Mobility
- Growth (weight gain)

Challenges: Why is progress so slow, and disease by disease?

Regulatory discussions and challenges

Clinical efficacy must be demonstrated by a measurement that is :

- Clinically objective
- Clinically meaningful

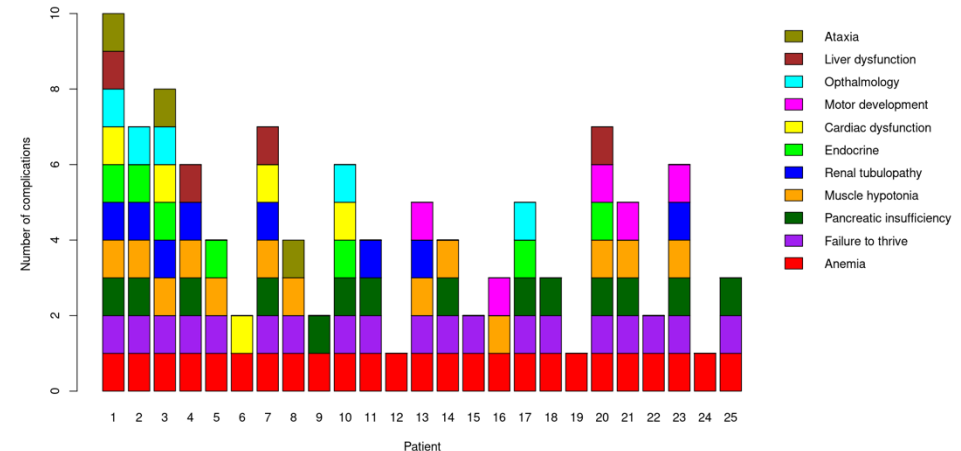
Basket vs single indication

- No measurement shared by multiple diseases
- Even challenging to find a measurement shared by just PS due to heterogeneity

Endpoints considered:

- IPMDS
- anemia
- height (change in height SDS)

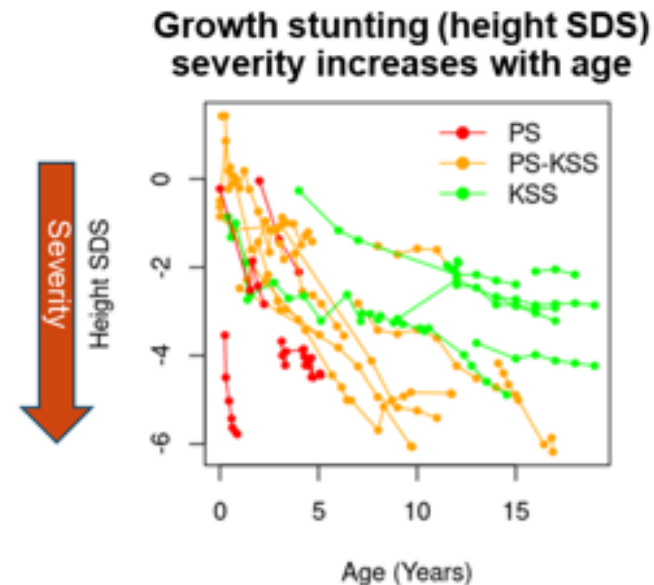
Pearson's Syndrome Multi-Systemic Phenotype



Adapted from Yoshimi *Brit J Haematol* 2021

Height SDS identified as clinically objective endpoint for clinical trial purposes

- Sponsored natural history study to identify measure to use for clinical trial development
- **Natural history shows continual decline in height SDS in PS and PS-KSS patients** (Ganetzky 2025)
- Height is clinically objective
- Height SDS reductions are likely indicative of **multiple organ dysfunction** (anemia, GI, pancreatic, appetite, wakefulness)
 - Use clinically objective measures of these organ systems to demonstrate it is clinically meaningful

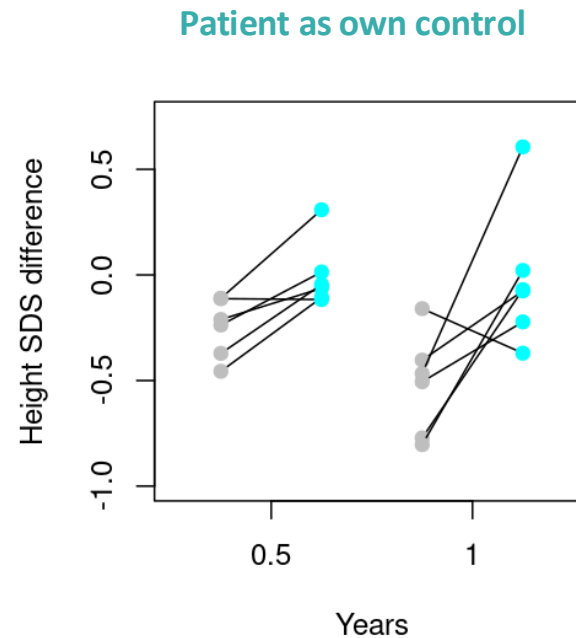
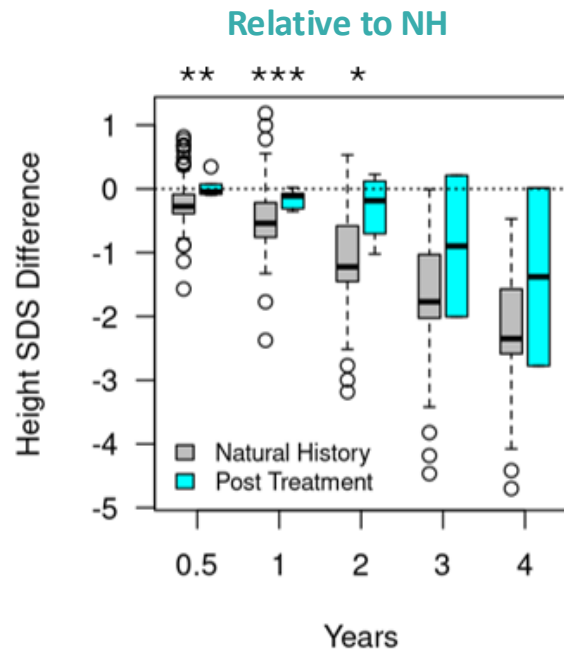


Change in height is meaningful for the Pearson Syndrome patients, not because it in itself is the biggest challenge, but as it can measure organ dysfunction in a patient population with heterogeneous organ involvement

First generation product demonstrated improvement or stabilization in height SDS relative to NH

Patients treated with MNV-101 show reduced growth stunting relative to pre-treatment measurements

- **Nine Pearson-KSS patients treated under CU and CT (4-8 years ago)**
- **MAT improves or delays deterioration in failure to thrive (FTT) measurement relative to natural history (NH) and patient as their own control (measured by height SDS)**



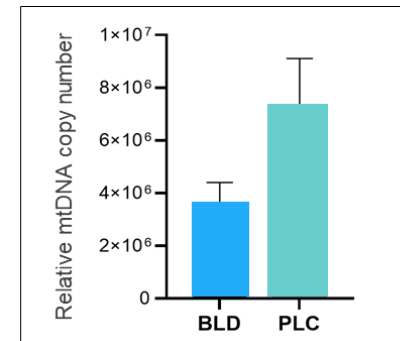
Height related parameters can be an endpoint for clinical trials in PS (not KSS).

Effect seems to be for at least one year, sometimes longer, but a single treatment is likely not sufficient

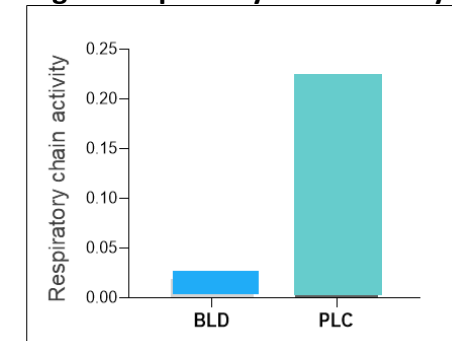
Transition to Allogeneic Mitochondria Product (AMP) from placenta

- Commercial scale, non-personalized
- Enables treatment of inherited or acquired diseases of mitochondrial dysfunction
- Higher potency
 - Higher mitochondrial activity
 - Higher genetic load
- Ability to track persistence in clinic – important for mechanistic understanding

Placental mitochondria exhibit higher mtDNA copy number



Placental mitochondria exhibit higher respiratory chain activity

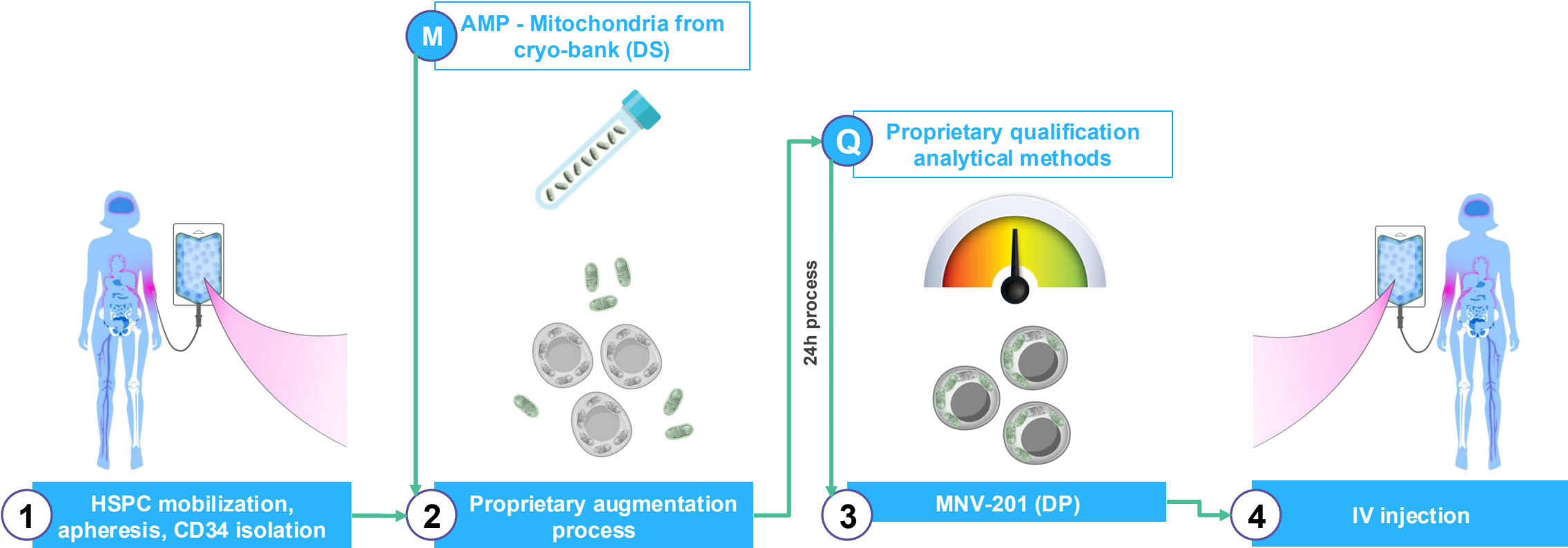


Implications for patients of Syngeneic to Allogeneic Transition

- Expansion to additional disease indications
- Is matching of mitochondria required?
- Implications for patients previously treated with MNV-101

Lead Product: MNV-201 Autologous HSPC Enriched with Allogeneic Mitochondria

High safety profile, no conditioning, rapid manufacturing

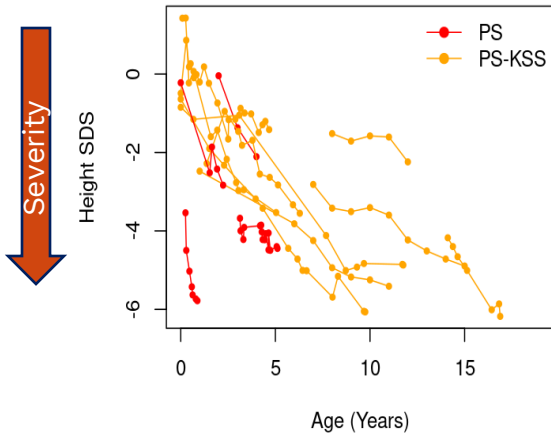


~72 hours vein-to-vein

Pearson's Syndrome patients treated with MNV-201 demonstrate safety and improvement in parameters of disease severity

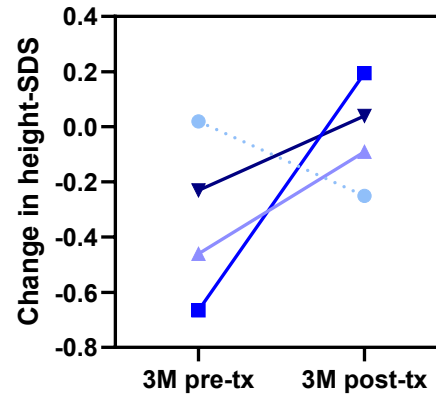
Natural History Data

Growth stunting (height SDS) severity increases with age

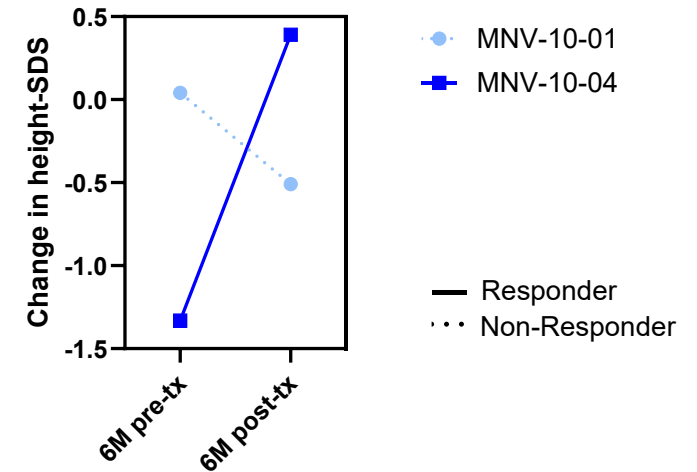


MNV-201 Follow Up

3m follow up



6m follow up



Follow-ups in clinical trials are critical to assess improvement and to support FDA approvals

Safety of MNV-101 and MNV-201 in PS

Overall, the products have a promising safety profile

- Definition of serious adverse event (SAE): undesirable experience associated with the use of a medical product
 - SAEs may be events that are life-threatening, require hospitalization (initial or prolonged), can lead to disability or permanent damage, or death
 - Somewhat confusingly they can be mild, moderate, or severe (for example – hospitalization for a mild condition)
- Definition of related to treatment
 - definitely related, probably related, possibly related, unlikely related, or unrelated

Clinical Mitochondrial Augmentation Technology: Positive Safety and Efficacy Profile in Two Indications

A total of 26 patients treated to date with MNV-101 and MNV-201 with multiple indications

Pearson's Syndrome

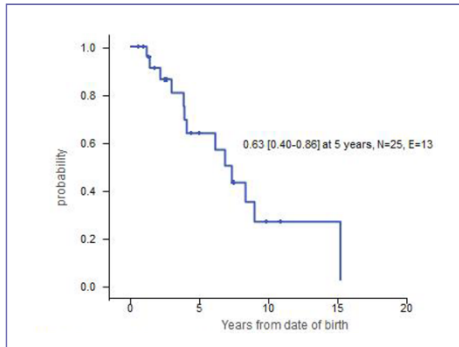
Rare pediatric, Accelerated approval pathway (PRV eligible)

Lethal pediatric disease caused by deletions of mtDNA, causing sideroblastic anemia, bone marrow and multi-organ failure

Low Risk MDS

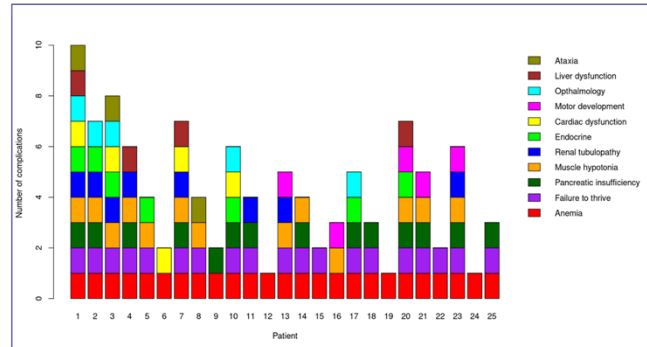
Mitochondrial dysfunction in HSPCs inhibits ability for blasts to differentiate in bone marrow causing MDS, and, in some instances, sideroblastic anemia

Pearson's Syndrome Survival Curve



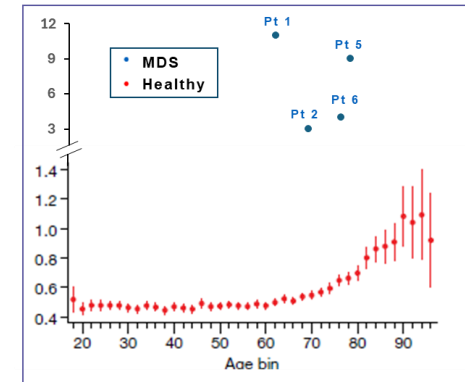
Adapted from Yoshimi *Brit J Haematol* 2021

Pearson's Syndrome Multi-Systemic Phenotype



Adapted from Yoshimi *Brit J Haematol* 2021

SNV mtDNA heteroplasmy count per individual across age groups

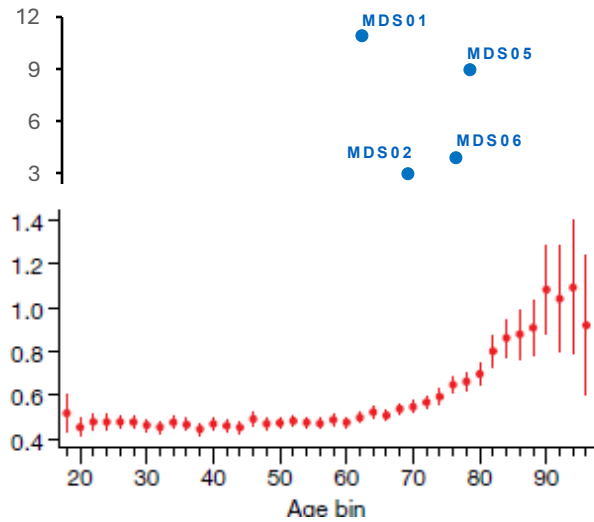


Adapted from Gupta *Nature* 2023

To date, MNV-201 has a positive safety profile in two disorders associated with mitochondrial dysfunction, including redosing.

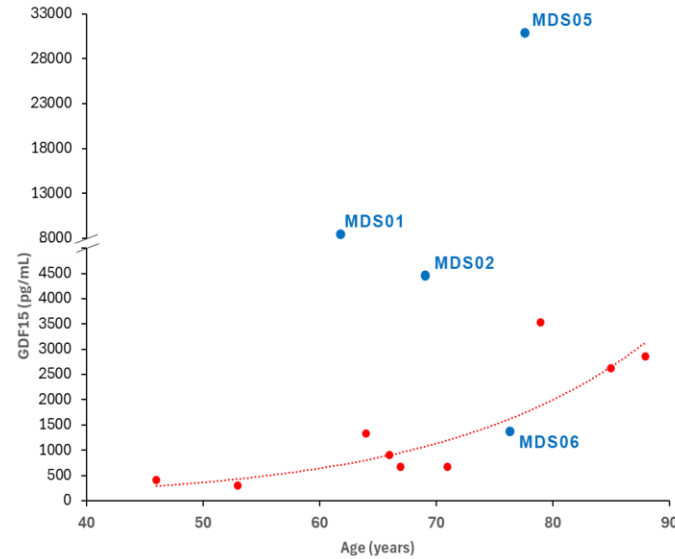
Mitochondrial biomarkers provide evidence that MDS is a mitochondrial disease

Mean SNV heteroplasmy count per individual across age groups

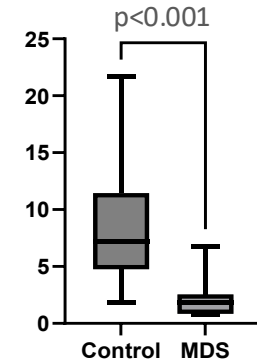


Adapted from Gupta Nature 2023

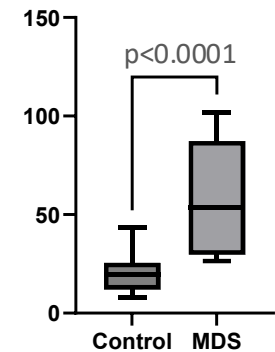
GDF15 per individual across age groups



MitoScore



Glycolytic Score



What is next for MNV-201?

- PS:
 - Phase 2 study ongoing in Israel (4 of 6 recruited)
 - Natural history study to provide sufficient data for FDA approval of endpoint and as run-in to pivotal trial
 - Regulatory alignment with the FDA on pivotal trial design
 - Technology transfer to US
- MDS
 - Phase 1 study ongoing in Israel
- Biomarker development to track mitochondrial function:
 - Use as follow up for patients treated
 - Understand which diseases or patient subsets have underlying mitochondrial dysfunction for further MNV-201 development

