AVROBIO

ASGCT 2022 Cystinosis data update

MAY 17, 2022

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POWERED BY AVROBIO plato

Expanding Phase 1/2 data set shows systemic gene therapy impact

AVR-RD-04 is *first and only* investigational gene therapy for cystinosis

All five patients dosed remain off oral cysteamine

- Improvements in neurocognitive assessments
- Stable muscle/grip strength
- Reduction in cystine crystals in skin and gastrointestinal mucosa
- Improved or stable eye measures
- Reduction in leukocyte cystine to target levels
- Quantified increase in hair strand pigmentation

Safety and tolerability profile remains strong*

Proof-of-concept demonstrated in adult population

Plan to meet with regulators in 2H 2022 to discuss company-sponsored trial

** Data as of May 6, 2022*

Cystinosis is an attractive commercial market

SOC is burdensome

- Shortcomings of cysteamine pills often lead to poor patient compliance:
  - Cause sulfur odor on body and breath
  - High daily pill burden can lead to GI discomfort and vomiting

SOC does not stop disease progression

Disease symptoms persist despite SOC:

Kidney function
Frequently require multiple kidney transplants

Vision
Corneal cystine accumulation, photophobia

CNS and muscular complications
Myopathy, hypotonia, neurodevelopmental issues

Endocrine disorders
Softening & deformation of bones, hypothyroidism, diabetes, infertility

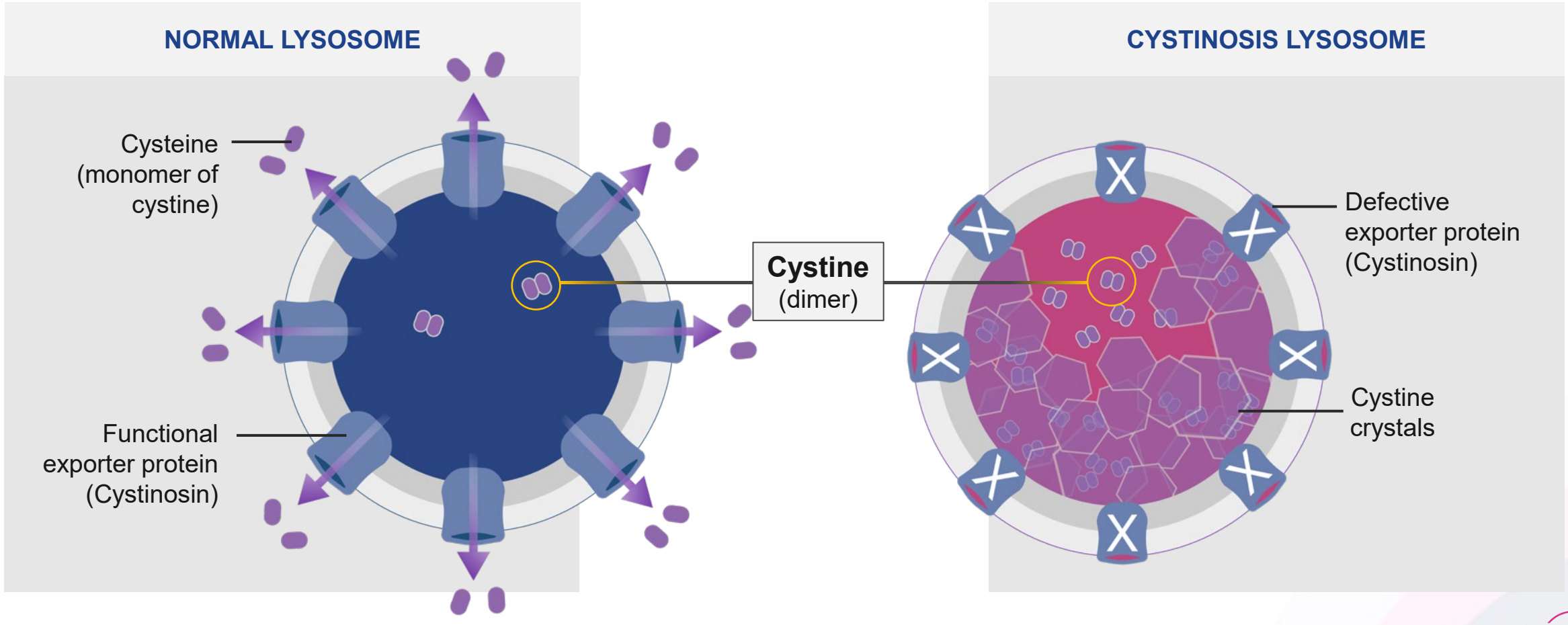
Billion-dollar revenue opportunity

- 5-year cystinosis SOC treatment cost ~$4.3 million* in U.S.
- ~1,600 patients in U.S., Europe and Japan alone
- Most severe form, infantile nephropathic cystinosis, affects ~95% of cystinosis population

** SOC: standard of care; WAC pricing from Redbook using standard dosing assumptions. Horizon's Procysbi oral therapy (delayed release cysteamine bitartrate), midpoint between avg. adult and pediatric*

Cystinosis caused by defective gene that encodes cystinosin, an exporter protein

Cystine crystals build up in lysosomes causing tissue and organ damage



Source: Cherqui et al, Nat Rev Nephrol. 2017

All patients continue to be oral cysteamine-independent

Patient #1 out 2 ½ years

NEW DATA

	PATIENT	MONTHS OFF CYSTEAMINE PILLS AND EYE DROPS POST AVR-RD-04 INFUSION	CURRENT STATUS
cysteamine pills	PATIENT 1	31	OFF
	PATIENT 2	22	OFF
	PATIENT 3	17	OFF
	PATIENT 4	5	OFF
	PATIENT 5	1	OFF
cysteamine eye drops	PATIENT 1	31	OFF
	PATIENT 2	13	ON (patient restarted July 2021)
	PATIENT 3	17	OFF
	PATIENT 4	Was not on cysteamine eye drops prior to infusion	OFF
	PATIENT 5	1	OFF

Note: Patients 2, 3 and 5 stopped cysteamine eye drops 1-month post-transplant (per protocol); Patient 1 stopped cysteamine eye drops prior to baseline; Patient 4 was not on cysteamine drops prior to infusion. Data as of May 6, 2022

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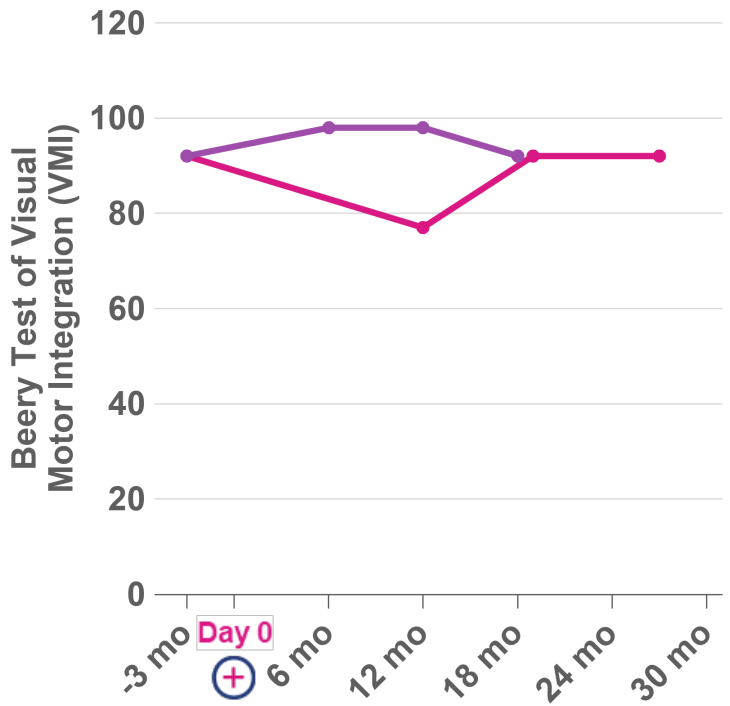
Improvement in motor coordination and visual perception observed post gene therapy

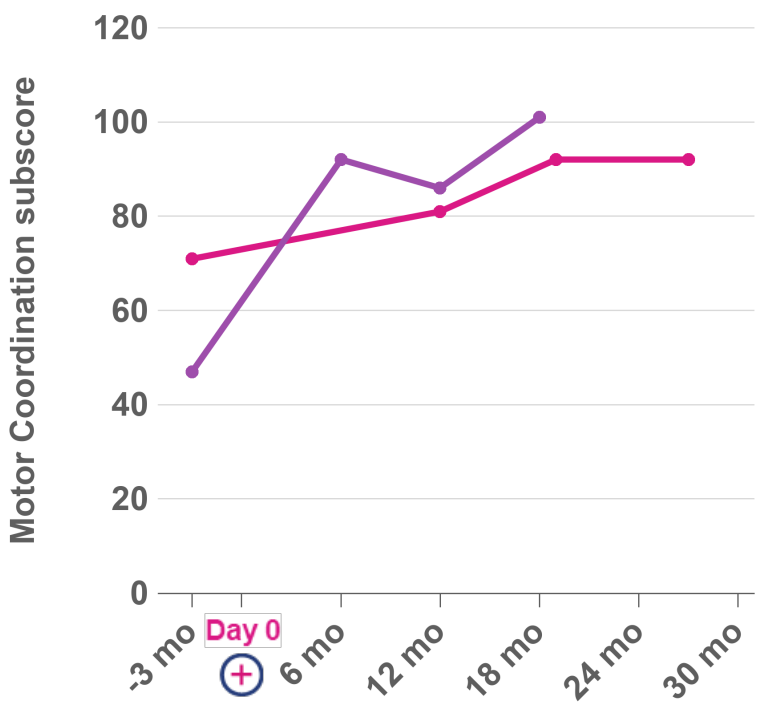
NEW DATA

Patient 1 Patient 3

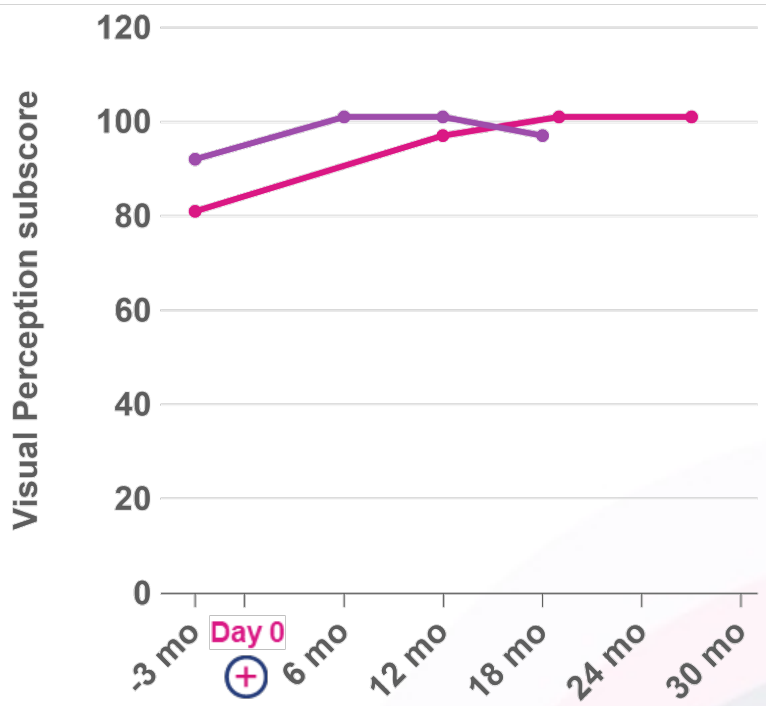
BEERY TEST OF VISUAL MOTOR INTEGRATION (VMI)



MOTOR COORDINATION SUBSCORE



VISUAL PERCEPTION SUBSCORE

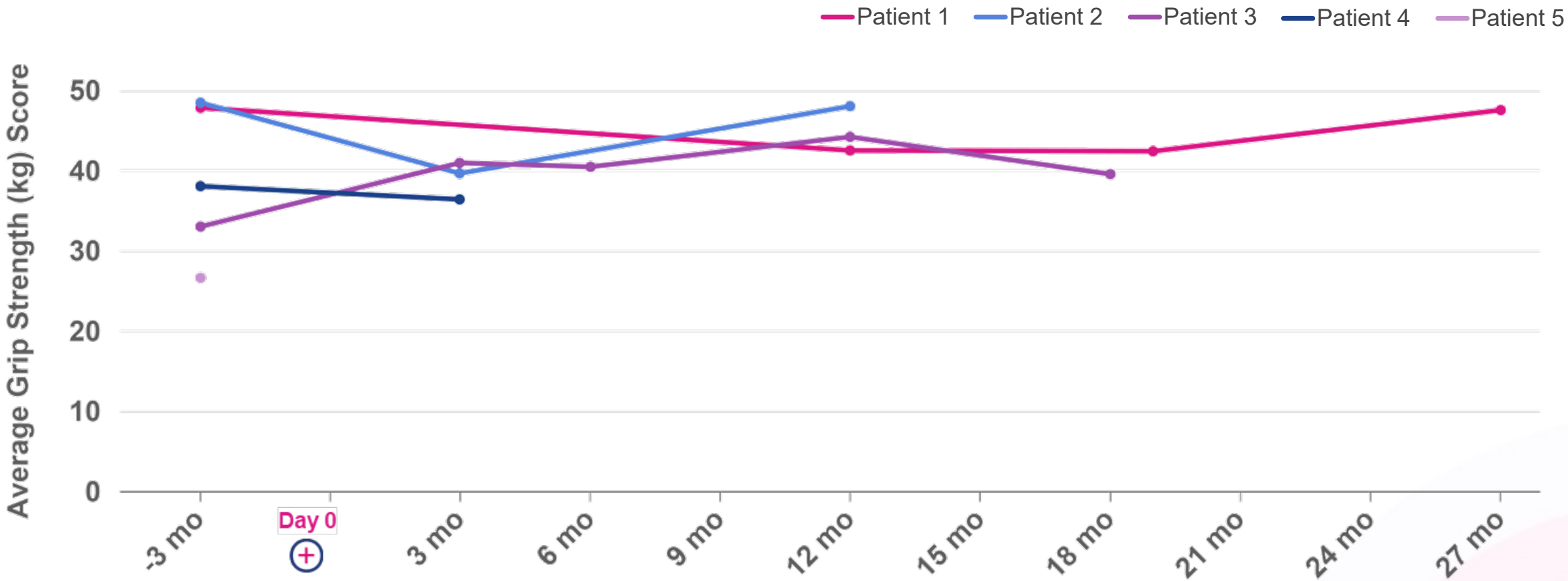


Data for Patient 2 are not available; The Beery – Buktenica Developmental Test of Visual Motor Integration (Beery VMI) is a standardized test evaluating the ability of the brain to interpret and translate visual information into an exact motor response

Average grip strength stable up to 27 months

Disease progression typically leads to loss of muscle strength over time

NEW DATA

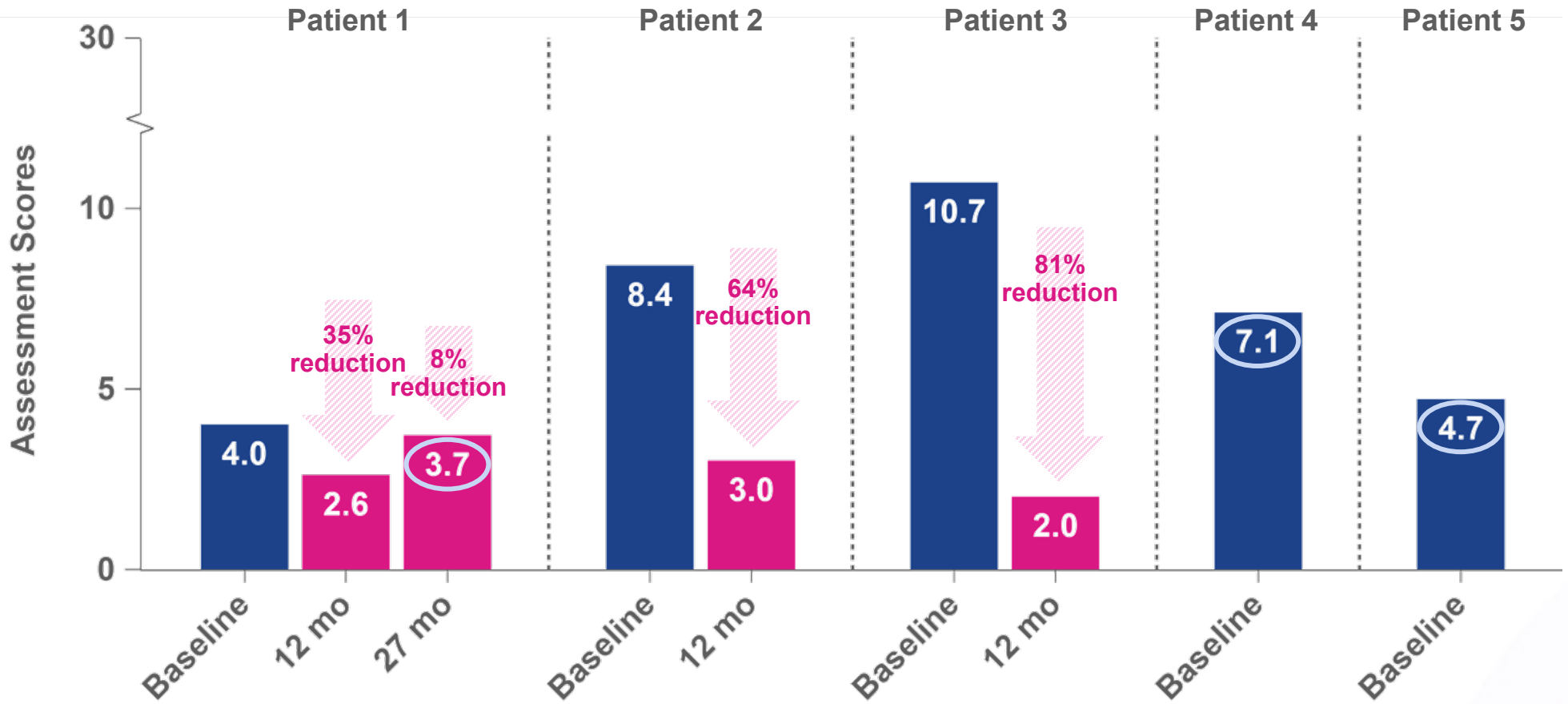


Average Grip Strength (kg) is defined as the average of the largest reading from each hand

Reduction in number of skin cystine crystals below patients' own SOC baseline at 12+ months

SKIN BIOPSY: AVERAGE INTRACYTOPLASMIC CRYSTALS PER CELL

NEW DATA POINT



For Patient 4 and 5, only their Baseline data is currently available

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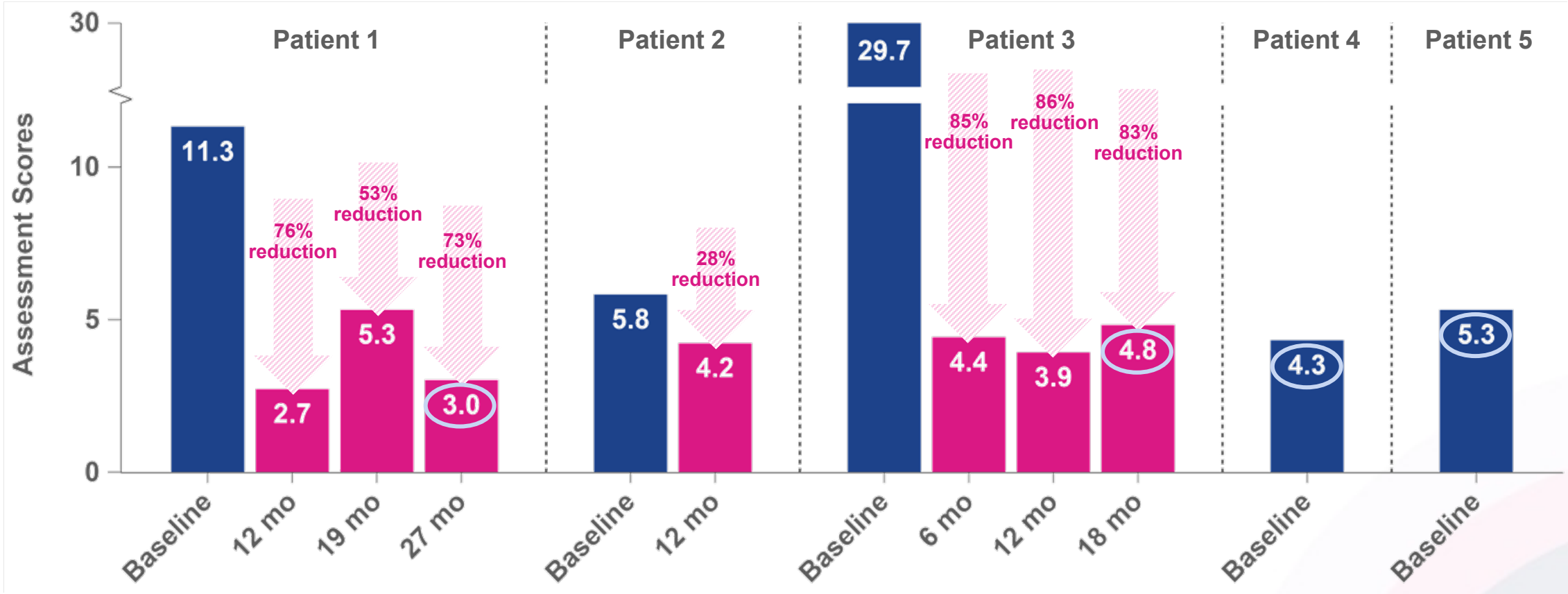
Reduction in number of cystine crystals in gastrointestinal mucosa below patients' own SOC baseline at 12+ months

RECTAL BIOPSY: AVERAGE INTRACYTOPLASMIC CRYSTALS PER CELL

NEW DATA POINT



For Patient 4 and 5, only their Baseline data is currently available

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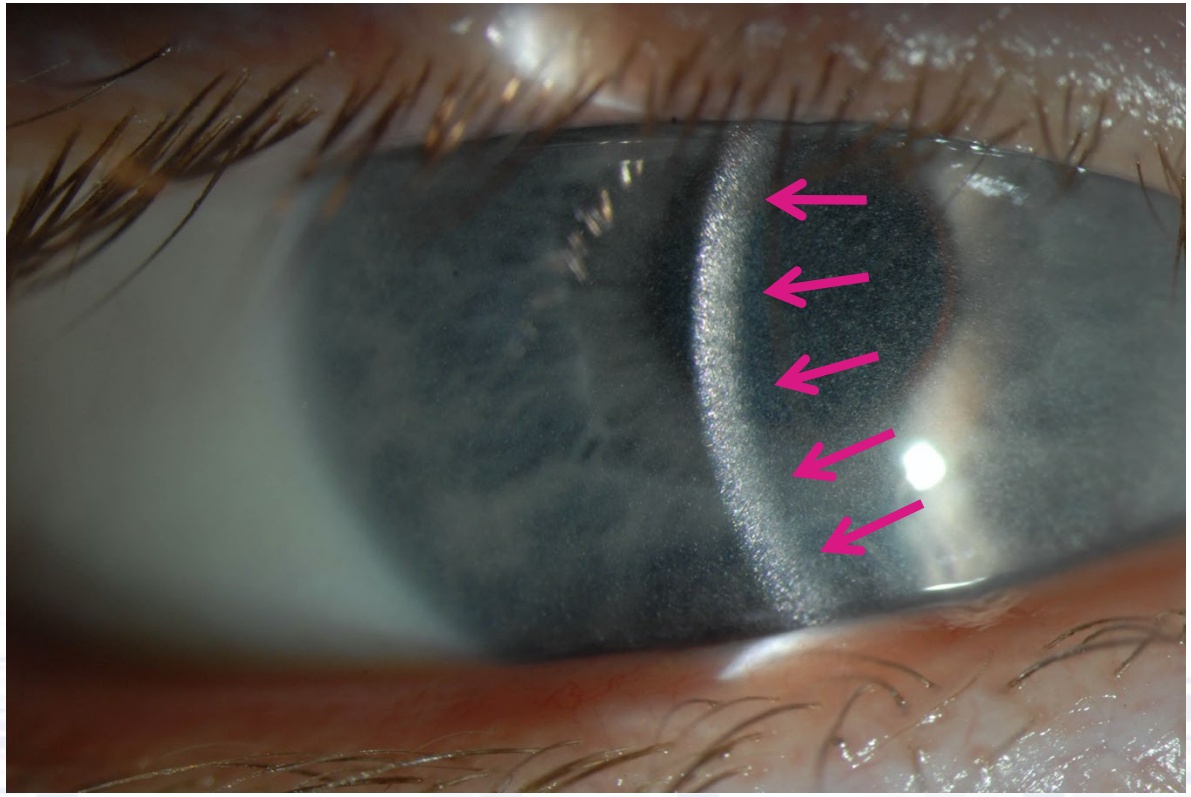
Crystal buildup in eye clearly visible before gene therapy

Treatment goal is to prevent or halt further accumulation of corneal crystals; complete clearance not expected

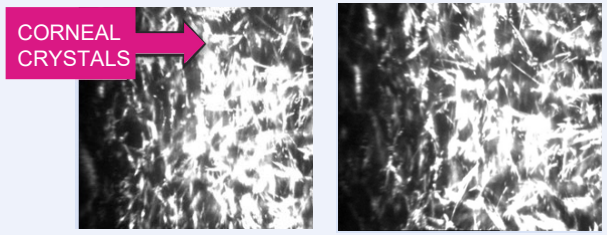


Patient 1 at baseline

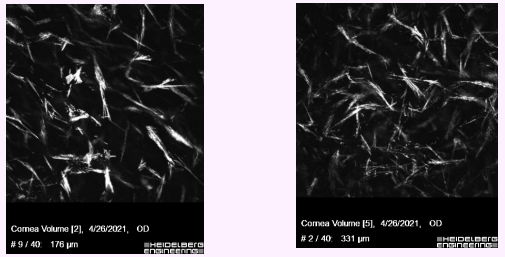
Decline in corneal crystals and improved photophobia grade

NEW DATA POINT

	BASELINE		18 MONTHS IMAGES/24 MONTHS PHOTOPHOBIA GRADE	
	IVCM Images	Photophobia Grade* (patient reported)	IVCM Images	Photophobia Grade* (patient reported)
PATIENT 1	*Front* of Cornea ... *Back* of Cornea	3	*Front* of Cornea ... *Back* of Cornea	1



174 µm, OD *331 µm, OD*



176 µm, OD *331 µm, OD*

	Right eye		Left eye	
Eye layers	**Baseline**	**12 months**	**Baseline**	**12 months**
Anterior Stroma	4	3	4	1.9
Middle Stroma	4	3	4	1.7
Posterior Stroma	4	2.1	4	2

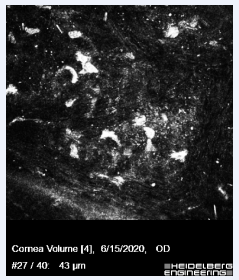
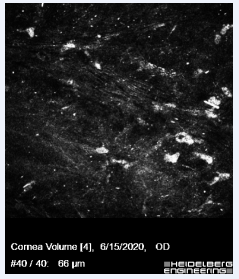
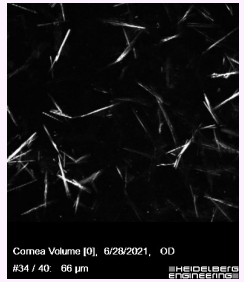
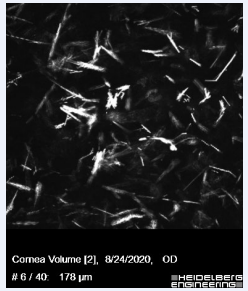
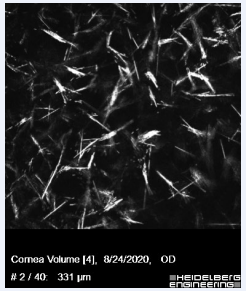
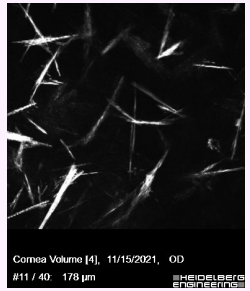
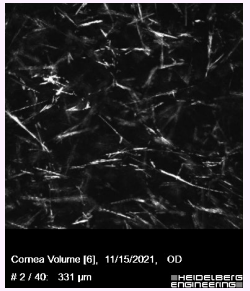
Preliminary scoring performed by Dr. Hong Liang

CNRS, Paris, France

*IVCM: In Vivo Confocal Microscopy; exploratory method; These results are for a single patient only and may vary in the study population; OD: Oculus Dexter (right eye); HRT3: Heidelberg Retina Tomograph 3; Scoring instructions: for each layer, assign a score of 0-4, where 0=no crystal; 1 <25%; 2=25-50%; 3=50-75%; 4>75%; Liang et al., IOVS 2015; * Score range: 1-5 where 1 is no photophobia and 5 is severe; Images obtained for Patient 1 at baseline using Nidek Confoscan and used Heidelberg HRT3 w/ Rostock Corneal Module for all other images*

Stable corneal crystals and photophobia grade

NEW DATA

	BASELINE		12 MONTHS	
	IVCM Images	Photophobia Grade (patient reported)	IVCM Images	Photophobia Grade (patient reported)
PATIENT 2	*Front* of Cornea:  43 µm, OD *Back* of Cornea:  66 µm, OD	2 or 3	*Front* of Cornea:  43 µm, OD *Back* of Cornea:  66 µm, OD	2
PATIENT 3	 178 µm, OD  331 µm, OD	2	 178 µm, OD  331 µm, OD	2

*IVCM: In Vivo Confocal Microscopy; exploratory method; These results are for a single patient only and may vary in the study population; OD: Oculus Dexter (right eye); HRT3: Heidelberg Retina Tomograph 3; Scoring instructions: for each layer, assign a score of 0-4, where 0=no crystal; 1 <25%; 2=25-50%; 3=50-75%; 4>75%; Liang et al., IOVS 2015; * Score range: 1-5 where 1 is no photophobia and 5 is severe;*

Early cystinosis treatment is essential to prevent kidney complications

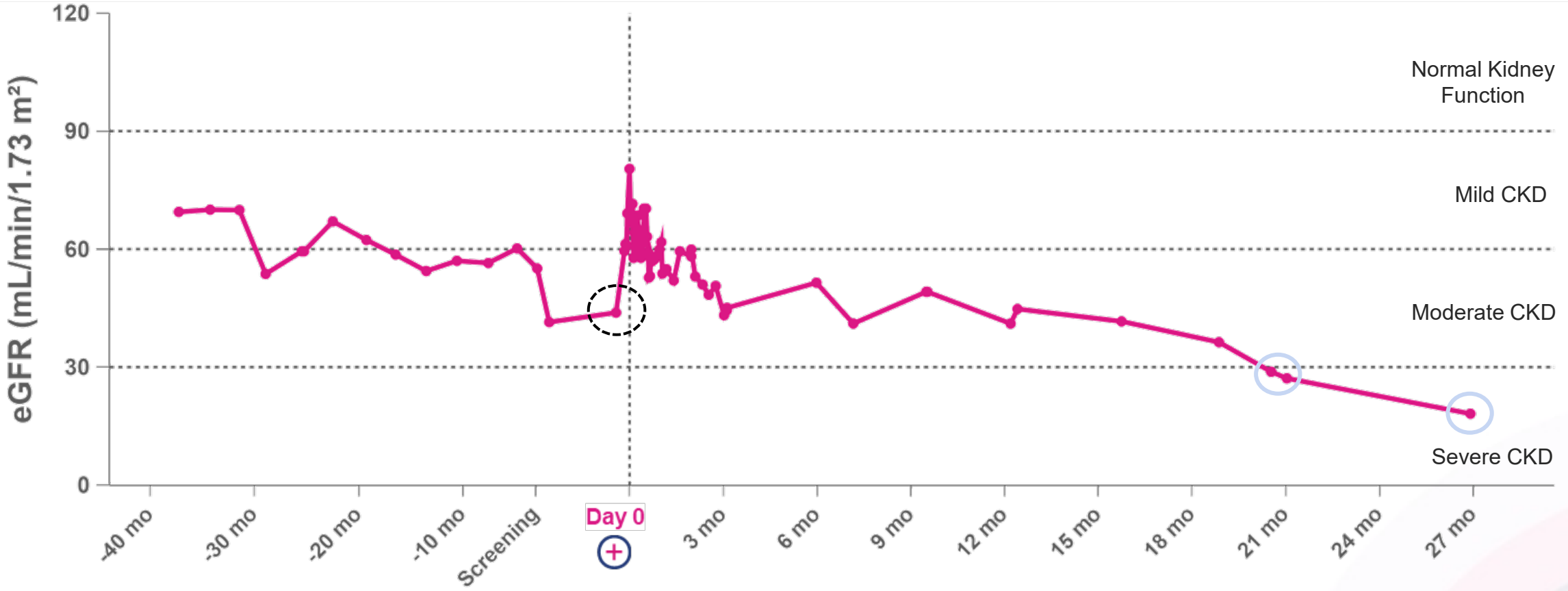
Disease phenotype	Nephropathic cystinosis	
	Infantile	Juvenile ("late-onset")
Frequency[1]	~95% of patients	<5% of patients
Characteristics of phenotype[1]	• Clinical symptoms related to renal Fanconi syndrome during **first year of life** – **Fanconi syndrome:** Defect of kidney tubules resulting in malabsorption of electrolytes / substances in kidneys[2] • Frequently require **multiple renal transplants with lifetime of immunosuppression** • **Most severe form** of cystinosis	• Usually diagnosed **later in childhood or during adolescence** (after age 10) • Typically experience **renal Fanconi syndrome and proteinuria** • Frequently require **multiple renal transplants with lifetime of immunosuppression**

Source: Simon-Kucher & Partners 2020. 1. Emma et al. (2014). Nephropathic Cystinosis: an international consensus document. Nephrology Dialysis Transplantation, 29(4), iv87-iv94; 2. Keefe et al. (2020). Fanconi Syndrome. StatPearls.

eGFR data reinforce need for early intervention

Entered trial with progressive kidney disease (eGFR of 48), decline accelerates in line with natural history

NEW DATA POINT

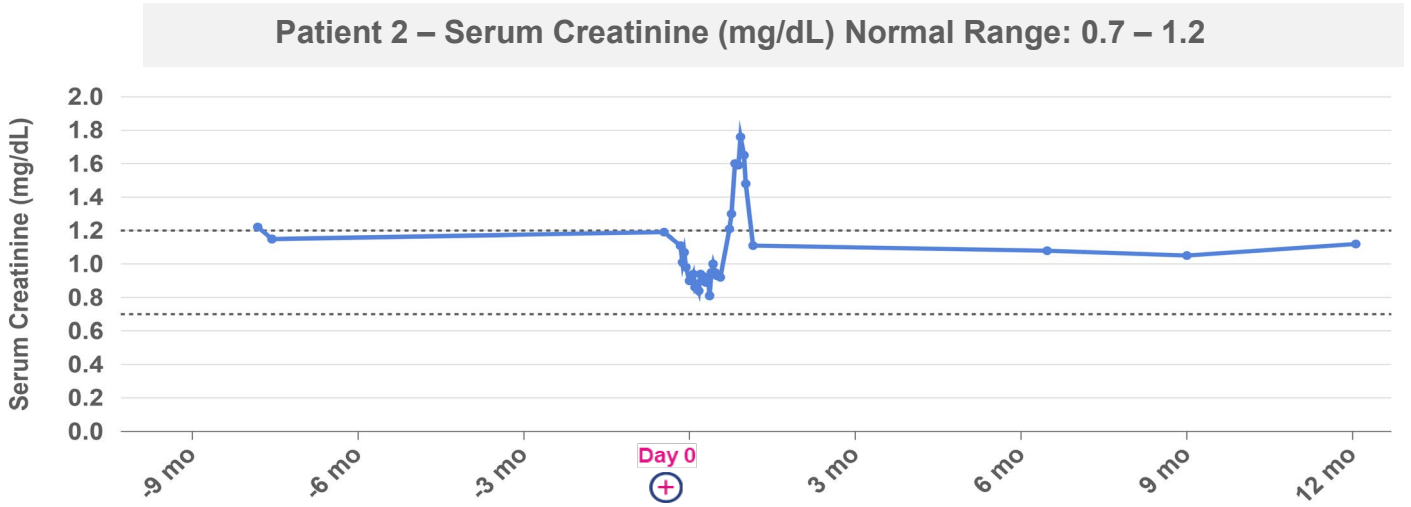


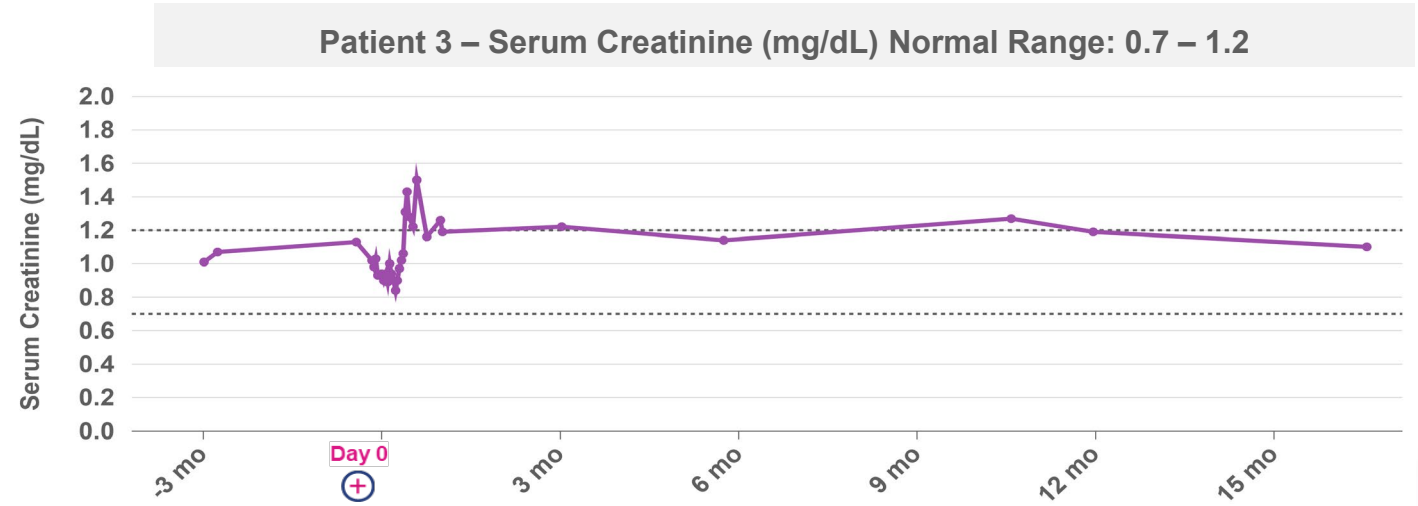
eGFR: Estimated Glomerular Filtration Rate; eGFR calculated using CKD-EPI formula

Transplanted kidney not impacted by treatment, as expected

Serum creatinine remains stable post infusion

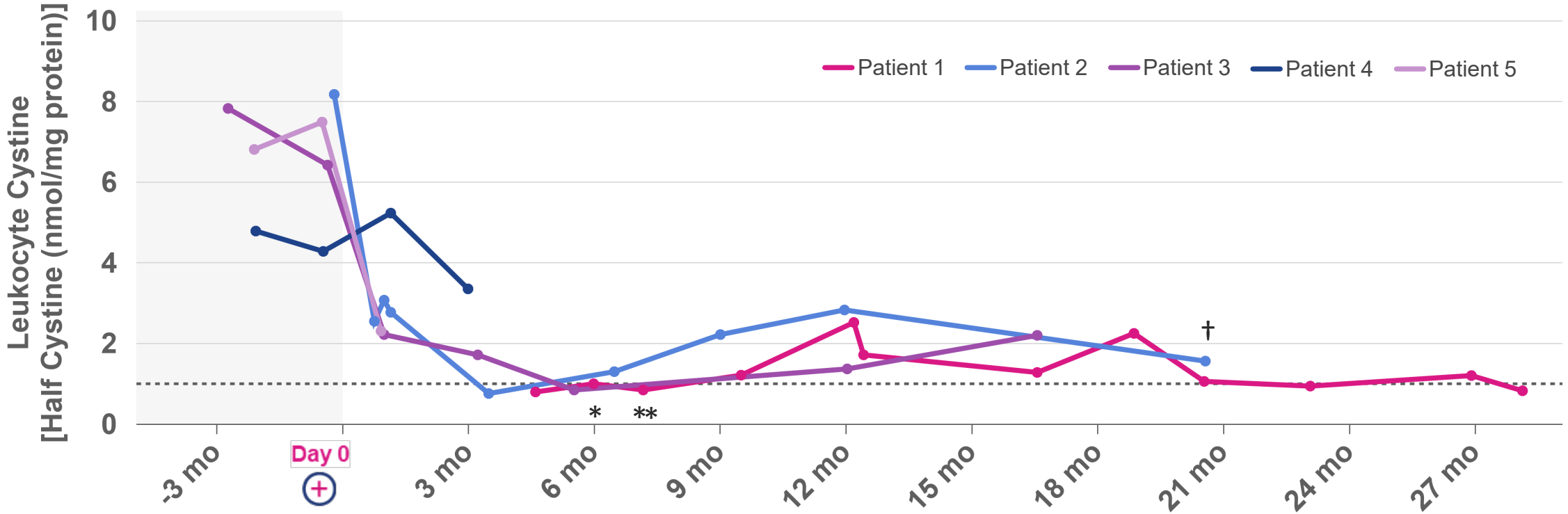
NEW DATA





Leukocyte cystine levels in blood suppressed out to 28 months

NEW DATA



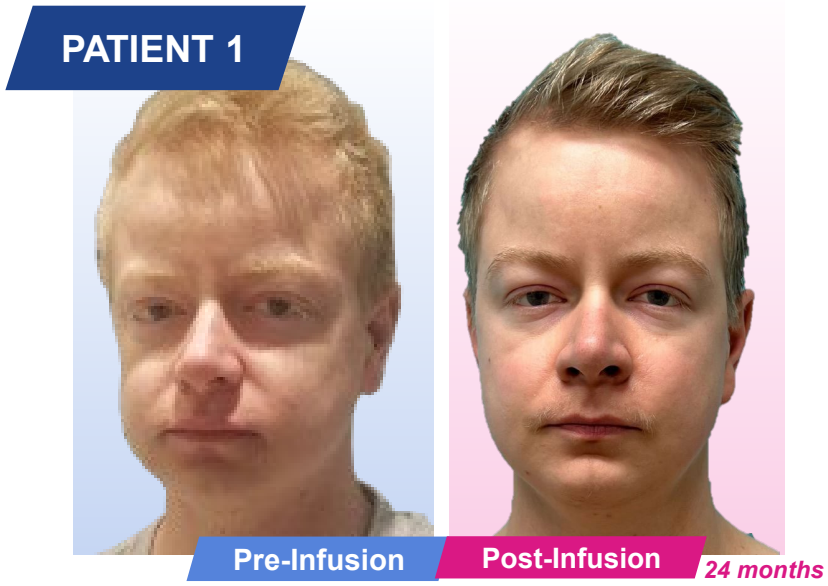
*Note: Data from Patient 1 up to 12 months have been previously disclosed. Therapeutic range is <1.0 Half Cystine (nmol/mg protein). Measure of 1 is level of healthy heterozygote.; For Patient 1, Leukocyte Cystine Quantification was initiated at approximately week 20 ; *Patient 1: Hemolyzed sample which may potentially lead to lower results; **Patient 1: Sample processed outside of the range of the stability; †Patient 2: Sample was not collected and shipped according to study protocol*

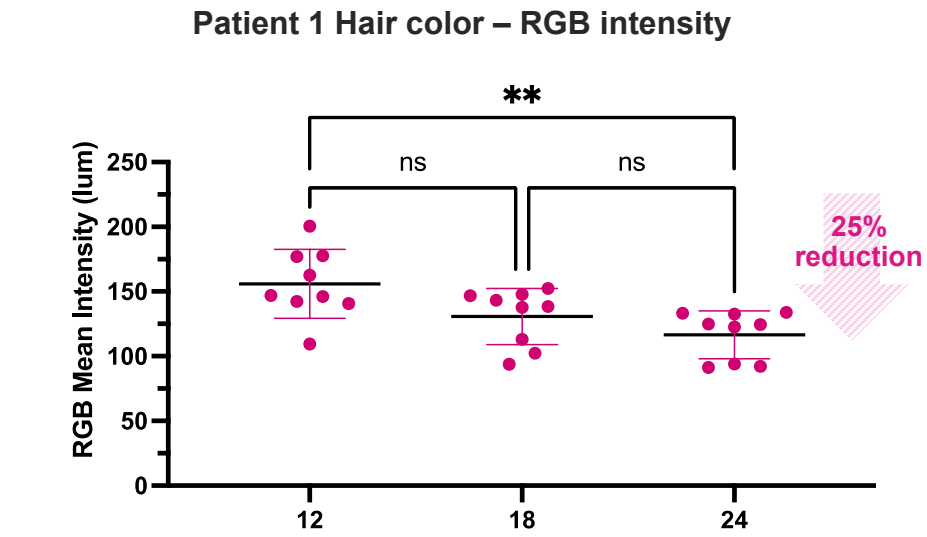
Darker pigmentation may be a sign of multi-functional cystinosin activity post gene therapy

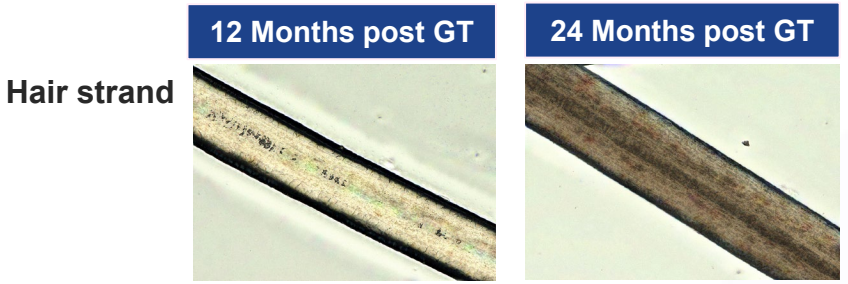
Further enforces systemic reach of gene therapy

NEW DATA

Cystinosin is located in melanosomes and regulates melanin synthesis







Note: GT: gene therapy; Source: Chiaverini et al., FESEB, 2012

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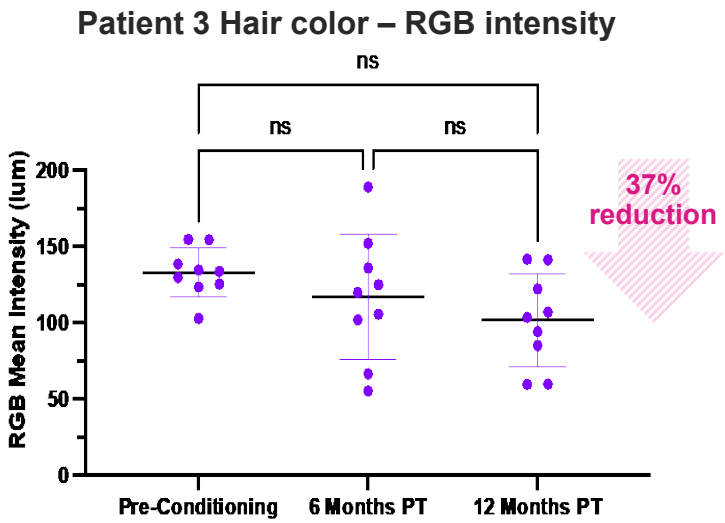
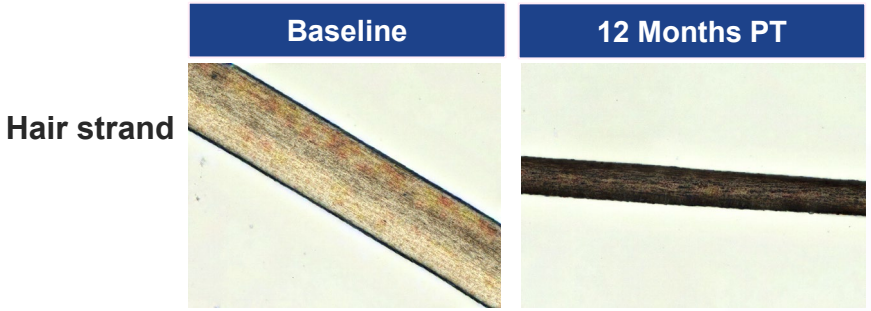
PATIENT 3*



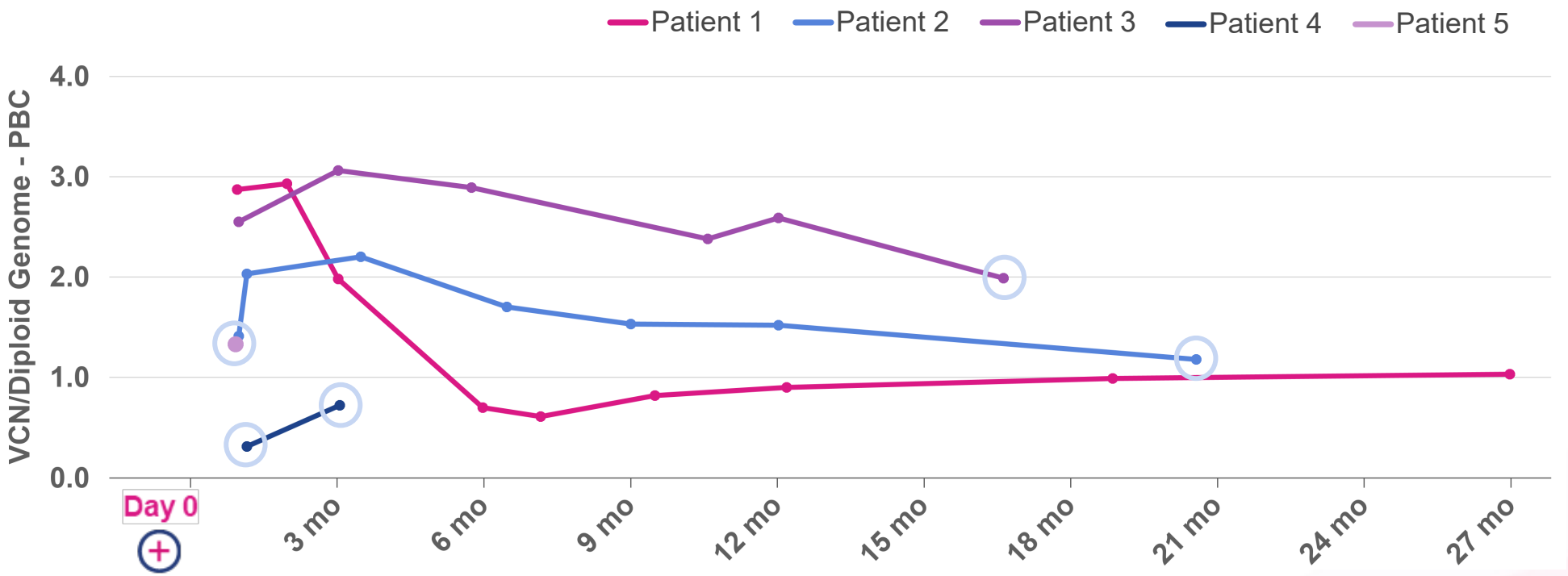


Source: Do not have permission to show patient image; Chiaverini et al., FESEB, 2012*

Sustained engraftment to date demonstrated by VCN plateau for patients beyond 12 months

NEW DATA POINT

Drug Product VCN/dg	
Patient 1	2.1
Patient 2	1.3*
Patient 3	1.6
Patient 4	0.6
Patient 5	2.5



** From second apheresis; VCN: Vector Copy Number; PBCs: Peripheral Blood Cells; dg: Diploid Genome*

Phase 1/2 Cystinosis trial
(5 patients)

No unexpected safety events or trends related to AVR-RD-04 identified

No SAEs or AEs related to AVR-RD-04 drug product

No SAEs reported

Preliminary AEs reported

- N=40 for subject 1; N=22 for subject 2; N=8 for subject 3; N=25 for subject 4; N=13 for subject 5
- Majority of AEs are mild or moderate
  - 1 severe -- Appendicitis unrelated to study treatment or procedures
- AEs generally consistent with myeloablative conditioning or underlying disease:

Pre-treatment and prior to conditioning (not all events listed)

- Diarrhea, hypokalemia, dizziness
- Dehydration, vomiting

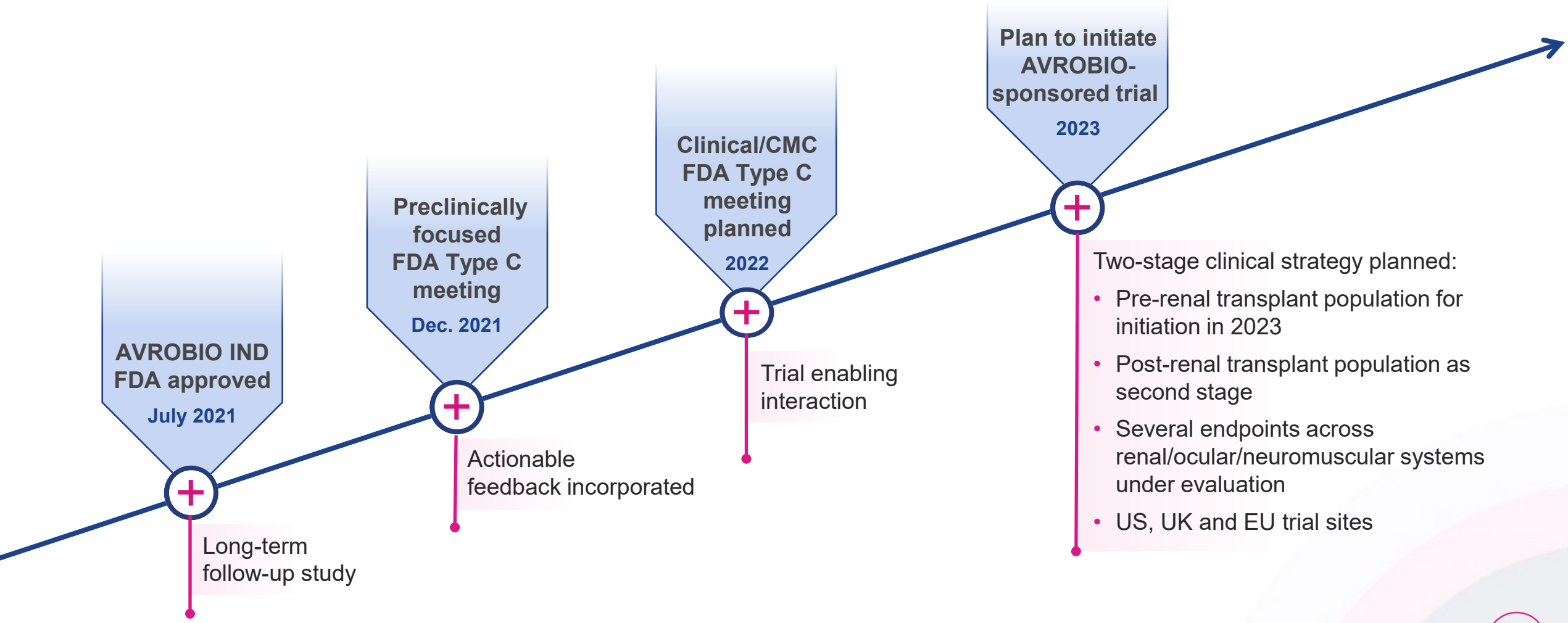
Post-treatment (not all events listed)

- Alopecia, intermittent diarrhea, vomiting, loss of appetite
- Mucositis, intermittent febrile neutropenia, intermittent epistaxis
- Intermittent blurry vision, intermittent hypokalemia, mucoceles
- Thrombocytopenia

AE: Adverse Event; SAE: Serious Adverse Event; safety data cut-off date is May 6, 2022

Building regulatory momentum

Active IND with US/EU Orphan Designation and US Fast Track Designation



Expanding Phase 1/2 data set shows systemic gene therapy impact

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- Improved or stable eye measures
- Reduction in leukocyte cystine to target levels
- Quantified increase in hair strand pigmentation

Safety and tolerability profile remains strong*

Proof-of-concept demonstrated in adult population

Plan to meet with regulators in 2H 2022 to discuss company-sponsored trial

** Data as of May 6, 2022*

Appendix

Patient baseline characteristics

	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4	PATIENT 5
Age of symptom onset/diagnosis	0 year / 8 months	0 year / 6 months	4 years	6 years	8 months
Age dosed with CTNS-RD-04	20 years Infused October 2019	46 years Infused June 2020	22 years Infused November 2020	33 years Infused November 2021	31 years Infused March 2022
Gender	Male	Male	Male	Male	Female
Mutation	• 57-kb deletion • c.696dupC, p.Val233Argfs*63	• 57-kb deletion • c.473T>C, p.Leu158Pro	• c.18_21del, p.Thr7Phefs*7 • c.295_298del, p.Val99Ilefs*18	• 57-kb deletion • c.473T>C, p.Leu158Pro	• 57-kb deletion • c.414G>A, p.Trp138*
Kidney transplant status and cysteamine dosing prior to CTNS-RD-04 dosing	• No kidney transplant; stage 3 (moderate CKD) renal failure • On oral Cysteamine • On Cysteamine drops	• 2 renal transplants (1987 and 1999) • On oral Cysteamine • On Cysteamine drops	• 1 renal transplant (2010) • On oral Cysteamine • On Cysteamine drops	• 2 renal transplants (2008 and 2017) • On oral Cysteamine • Off Cysteamine drops	• No renal transplant; stage 3 (moderate CKD) renal failure • On oral Cysteamine • On Cysteamine drops
Manufactured CTNS-RD-04 product and busulfan dose	• 7.88 x 10e6 CD34+ cells/kg • VCN: 2.07 • 94% viability • AUC Bu: 81.8 mg.h/L	• 5.07 x 10e6 CD34+ cells/kg • VCN: 1.27 • 91% viability • AUC Bu: 86.7 mg.h/L	• 9.59 x 10e6 CD34+ cells/kg • VCN: 1.59 • 95% viability • AUC Bu: 90 mg.h/L	• 3.63 x 10e6 CD34+ cells/kg • VCN: 0.59 • 90% viability • AUC Bu: 88.5 mg.h/L	• 9.12 x 10e6 CD34+ cells/kg • VCN: 2.5 • 95% viability • AUC Bu: 88.2 mg.h/L