What if ONE GENE can change your entire world?

ASGCT 2023 cystinosis update

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Summary of key points

- Continued positive trends across multiple biomarkers and neurocognitive measures seen in Phase 1/2 collaborator-sponsored trial
- All patients remain off oral cysteamine, up to 36 months post-gene therapy
- Safety and tolerability profile remains strong
- Positive interactions with U.K. Medicines and Healthcare products Regulatory Agency (MHRA) and U.S. Food and Drug Administration (FDA) in Q1 2023
- Activities for a company-sponsored Phase 1/2 clinical trial are planned to be initiated in 2H 2023

Cystinosis Phase 1/2 dosing complete

Phase 1/2

Collaborator-sponsored
University of California, San Diego

Objectives

- Safety and tolerability
- Hypothesis generation of clinical efficacy endpoints

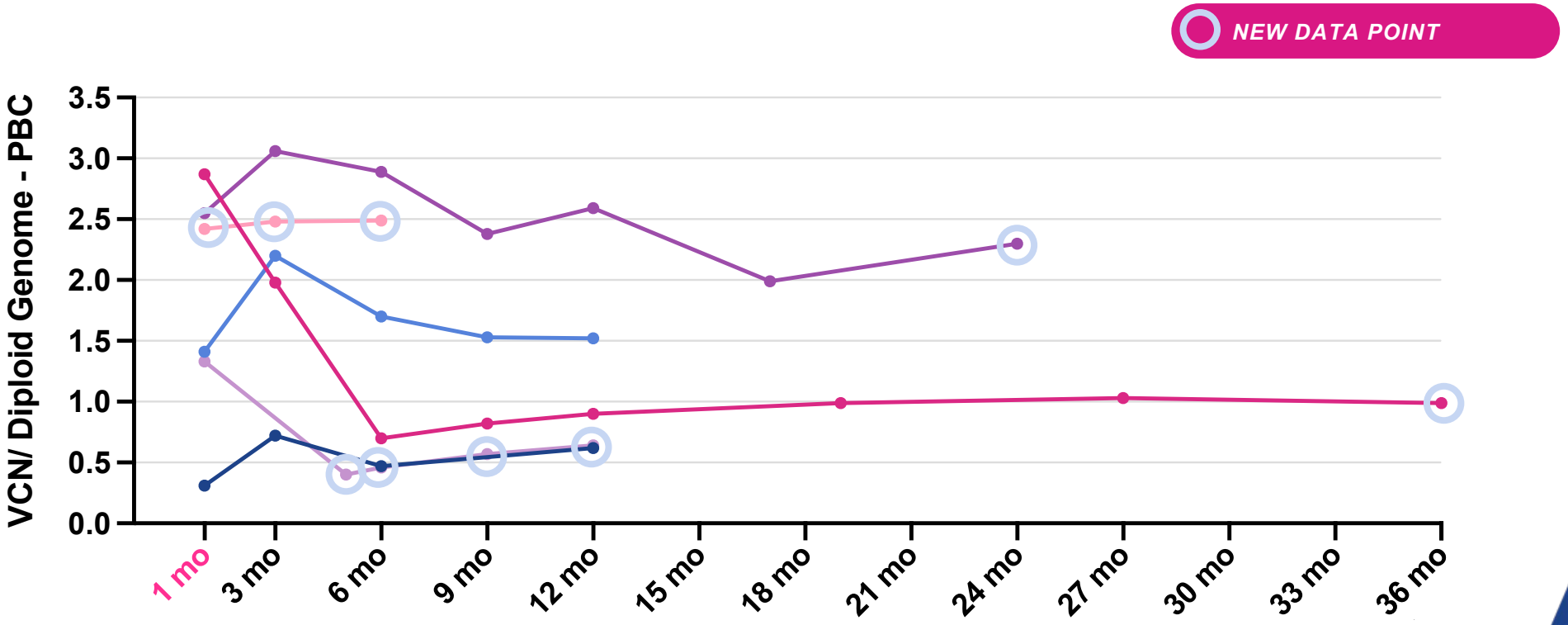
Patients

- 6 patients
- Adults and adolescents
- Cohorts 1-2 >18 years; Cohort 3 >14 years
- Male and female
- Oral and ophthalmic cysteamine

Clinical trial funded in part by grants to UCSD from the California Institute for Regenerative Medicine (CIRM), Cystinosis Research Foundation (CRF) and National Institutes of Health (NIH)

VCN trending as expected, indicating sustained engraftment

Drug Product VCN/dg	
Patient 1	2.1
Patient 2	1.3
Patient 3	1.6
Patient 4	0.6
Patient 5	2.5
Patient 6	2.9*



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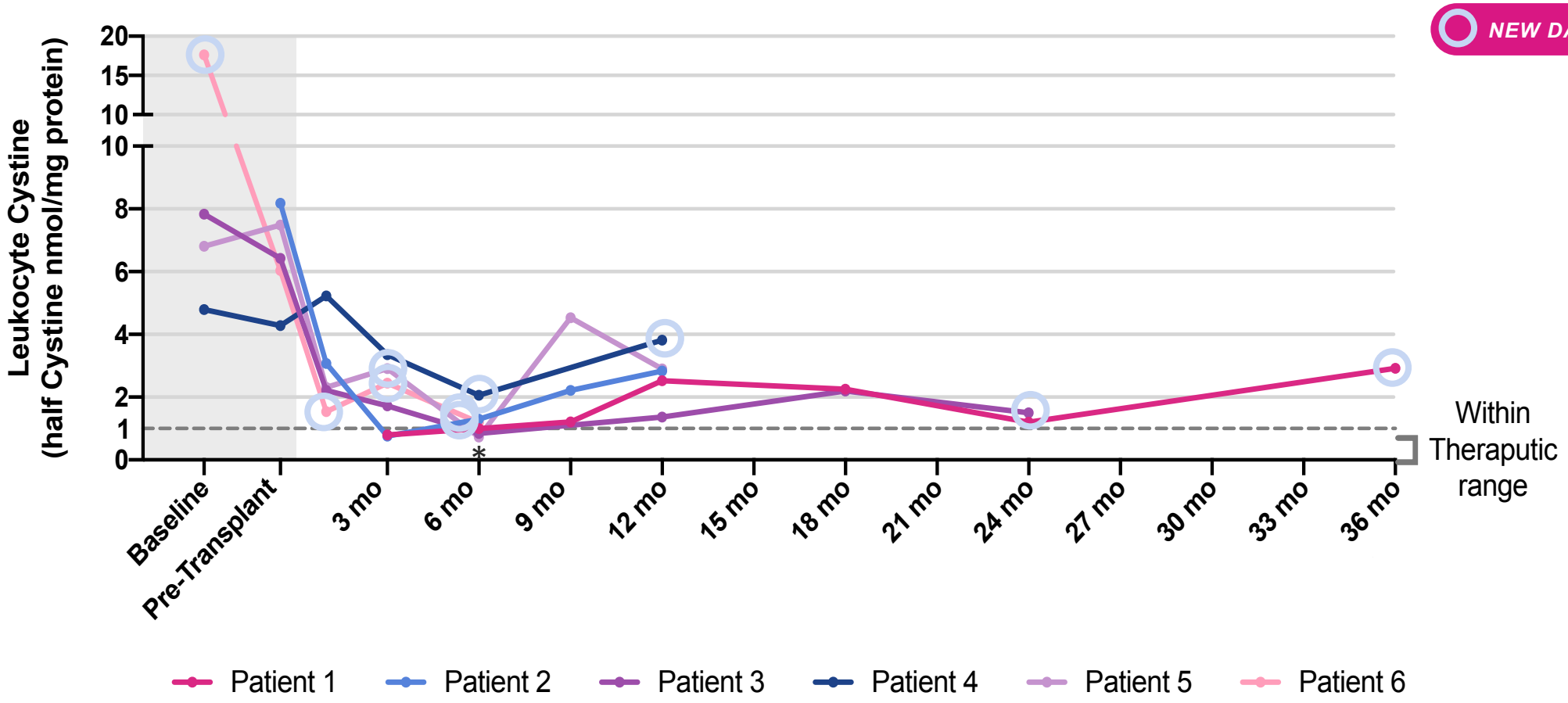
VCN: Vector Copy Number; PBCs: Peripheral Blood Cells; dg: Diploid Genome
*Average of 2 drug products
Note: Patient 2 was lost to follow-up after 12 months

Sustained leukocyte cystine level reduction

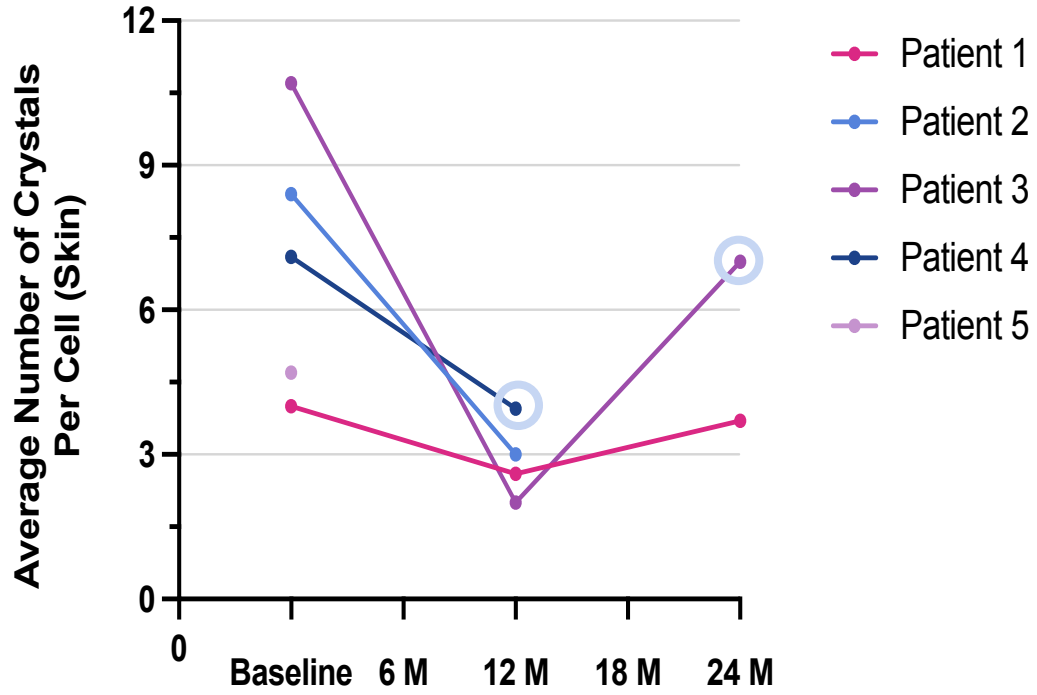


Therapeutic range is <1.0 Half Cystine (nmol/mg protein). Measure of 1 is level of healthy heterozygote.; For Patient 1, Leukocyte Cystine Quantification was initiated at approximately week 20 ; *Patient 1: Hemolyzed sample which may potentially lead to lower results; mo=month; Note: Patient 2 was lost to follow-up after 12 months

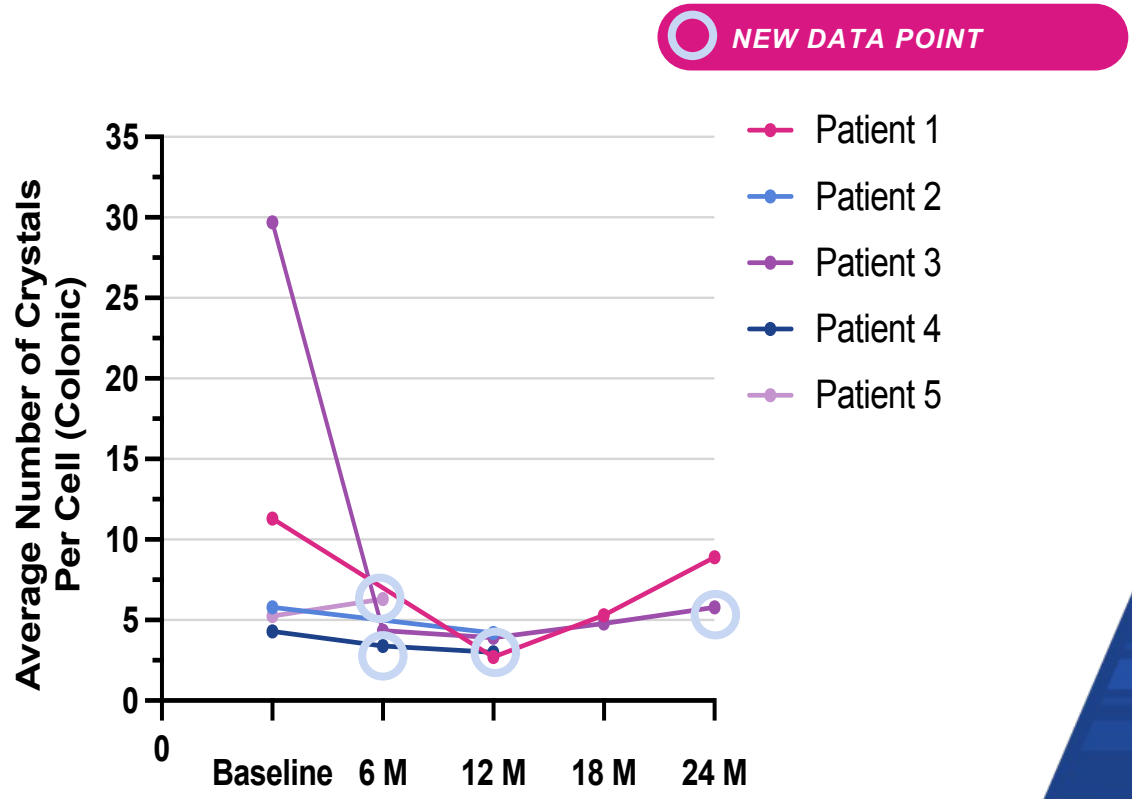
Skin and gastrointestinal mucosa cystine crystal reduction

Average intracytoplasmic crystals per cell

Skin Biopsy

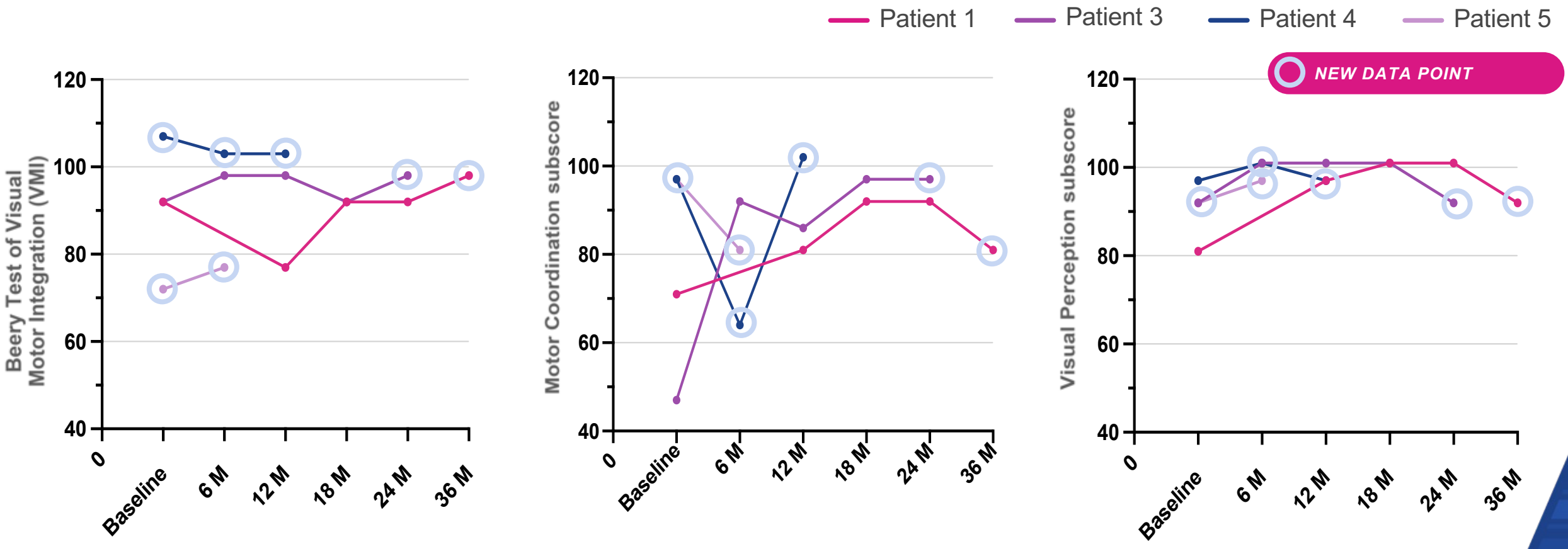


Rectal Biopsy



Note: Patient 2 was lost to follow-up after 12 months

Improvement or stabilization in motor coordination and visual perception



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The Beery – Buktenica Developmental Test of Visual Motor Integration (Beery VMI) [6th edition] is a standardized test evaluating the ability of the brain to interpret and translate visual information into an exact motor response; Patient 2 did not complete the examination

All patients continue to be oral cysteamine-independent

NEW DATA POINT

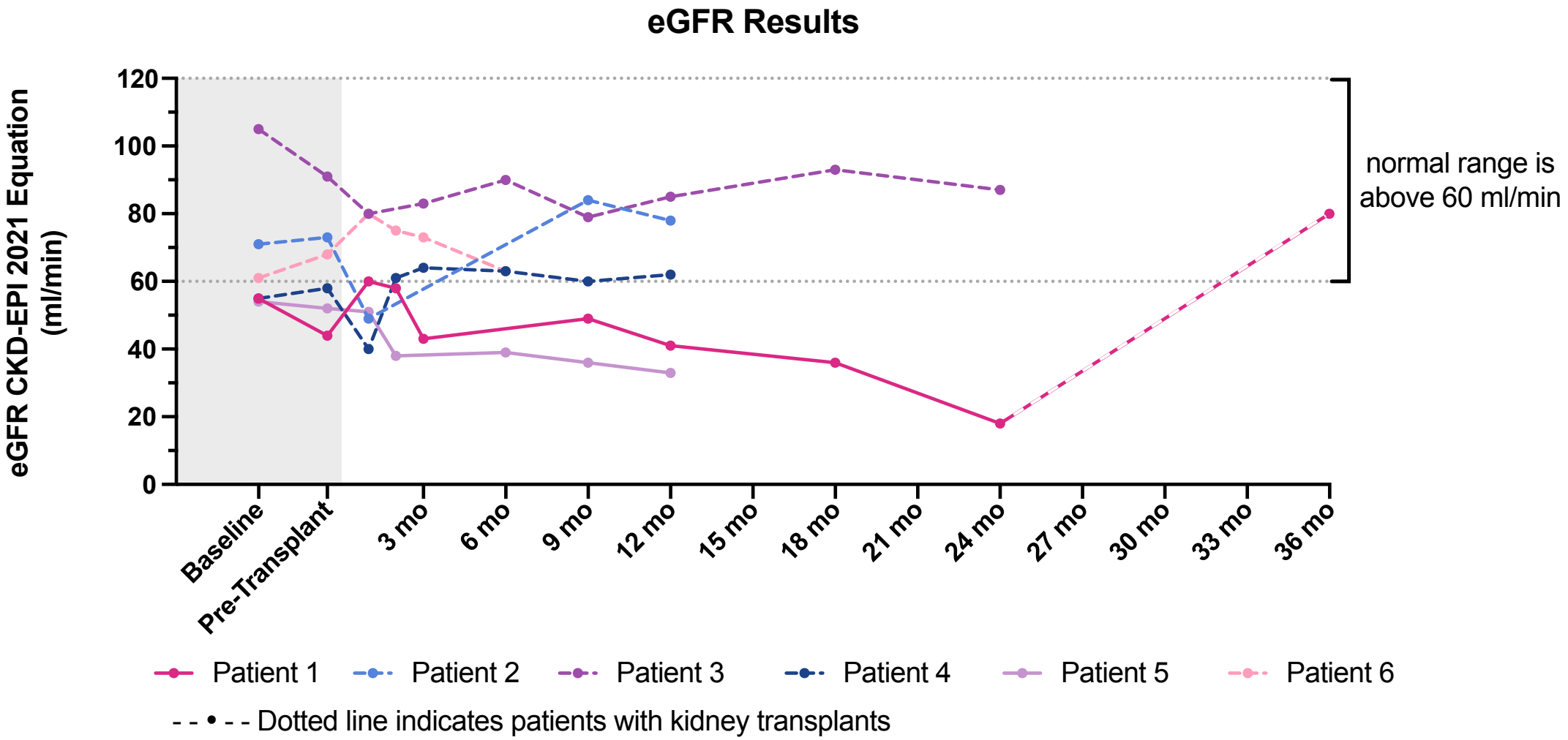
Patient #1 out 3 years

CYSTINOSIS PHASE 1/2: PATIENTS 1-6

	Patient	Months off cysteamine pills and eye drops post Ctns-rd-04 infusion	Current status
Cysteamine Pills	Patient 1	36	**OFF**
	Patient 2	12	**Lost to follow-up**
	Patient 3	24	**OFF**
	Patient 4	18	**OFF**
	Patient 5	12	**OFF**
	Patient 6	6	**OFF**
Cysteamine Eye Drops	Patient 1	36	**OFF**
	Patient 2	12	**Lost to follow-up**
	Patient 3	24	**OFF**
	Patient 4	Was not on cysteamine eye drops prior to infusion	**OFF**
	Patient 5	12	**OFF**
	Patient 6	6	**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; Data as of May 8, 2023.
Patient 2 has elected not to return since the 12-month follow-up visit.

eGFR data reinforce need for early intervention



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eGFR: Estimated Glomerular Filtration Rate; eGFR calculated using CKD-EPI formula
Note: Patient 2 was lost to follow-up after 12 months

No adverse events related to drug product

No SAEs or AEs related to drug product

No adverse events related to drug product

No SAEs reported

Preliminary AEs reported (as of May 8, 2023)

- N=46 for patient 1; N=22 for patient 2; N=8 for patient 3; N=29 for patient 4; N=37 for patient 5; N=41 for patient 6
- Majority of AEs are mild or moderate
- 1 severe AE for subject 1
    - Appendicitis (resolved) – unrelated to study treatment or procedures
- AEs are generally consistent with myeloablative conditioning, study procedures, underlying disease or co-morbid or pre-existing conditions:

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

- Diarrhea, hypokalemia, hypomagnesemia, thrombocytopenia, dizziness, dehydration, vomiting, bone pain, headache

Post-treatment (not all events listed)

- Pancytopenia, deep vein thrombosis, Staphylococcus sepsis, Coronavirus infection, alopecia, rash, mucositis
- Intermittent: diarrhea, vomiting, loss of appetite, epistaxis, blurry vision, febrile neutropenia, hypomagnesemia, hypokalemia

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AE: Adverse Event; SAE: Serious Adverse Event

Positive regulatory interactions

Overview

- Positive interactions with U.K. Medicines and Healthcare products Regulatory Agency (MHRA) and U.S. Food and Drug Administration (FDA) in Q1 2023
- Activities for a company-sponsored Phase 1/2 clinical trial planned to be initiated in 2H 2023
- Will initially evaluate pediatric, pre-renal transplant population with a focus on renal Fanconi syndrome

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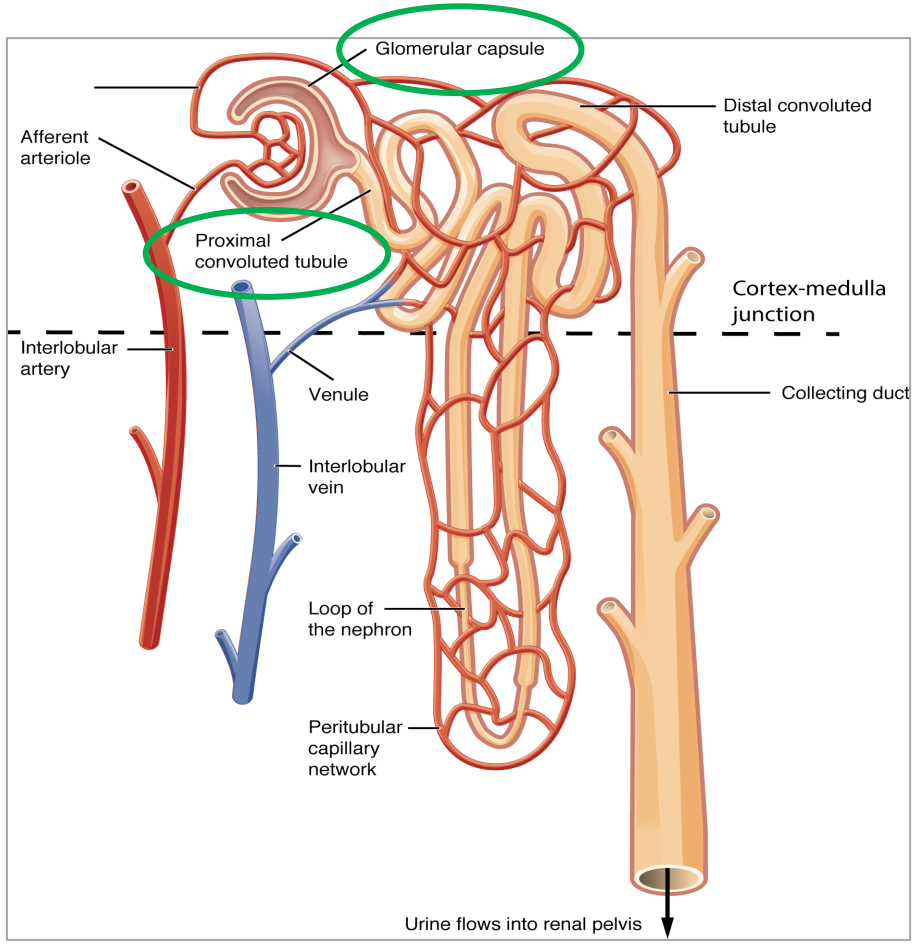
Planned RFS endpoint captures complexity of disease

Potential to *reverse* RFS by providing functional cystinosin

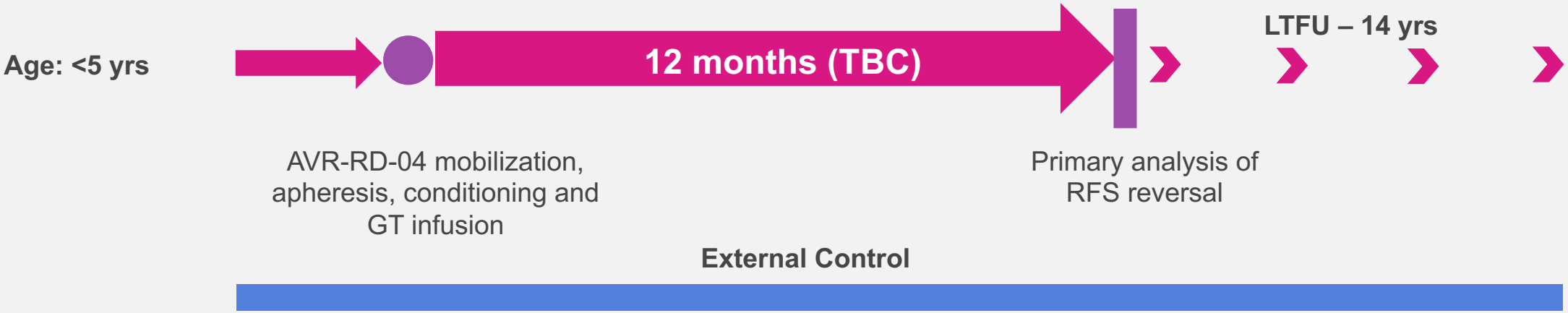
- RFS is hallmark of nephropathic cystinosis
  - Dysfunction of proximal tubules
  - Causes urinary losses of amino acids, LMW proteins and electrolytes
  - Cysteamine MOA does not address RFS
- Progressive loss of glomerular function leads to ESRD
  - Glomerulopathy manifests clinically with reductions in GFR
- Providing functional cystinosin reverses RFS and preserves renal function in CTNS -/- mice with syngeneic BM-derived stem cells
- AVR-RD-04 may partially or completely restore the proximal tubule physiology and *reverse* RFS



Syres 2009; Yeagy 2011, Gabriel 2017; RFS=Renal Fanconi Syndrome; LMW=Low molecular weight; ESRD=End-stage renal disease; BM=Bone marrow: MOA=Method of action; GFR=Glomerular filtration rate

Planned cystinosis company-sponsored clinical trial design

Single-arm trial designed to be registration-enabling, subject to regulatory alignment



PRIMARY AND SECONDARY EFFICACY ENDPOINTS: Focused on Change from Baseline to 12 months in reversal of RFS parameters

TWO-STAGE CLINICAL STRATEGY:

- Pre-renal transplant population planned for initiation in 2H 2023
- Post-renal transplant population as second stage

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GT=Gene therapy

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