UNIVERSITY of CALIFORNIA, SAN DIEGO
SCHOOL OF MEDICINE

Hematopoietic Stem Cell Gene Therapy for Cystinosis: updated results from a phase 1/2 clinical trial

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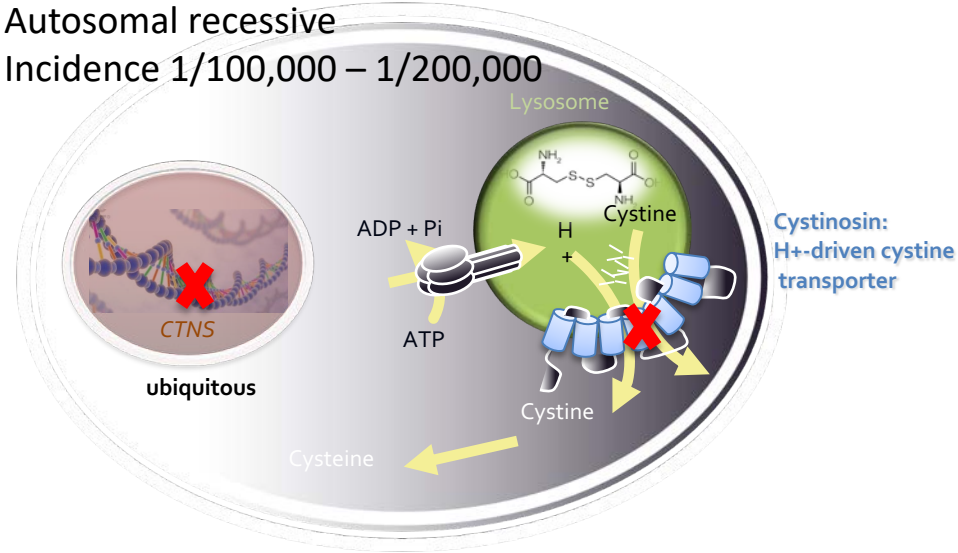
Professor, Department of Pediatrics

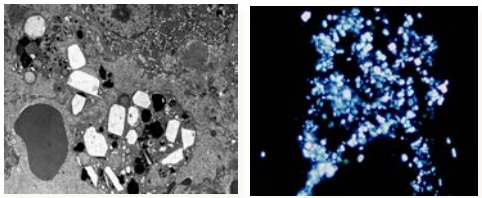
DISCLOSURE

- I am cofounder, shareholder and a member of both the scientific board and board of directors of Papillon Therapeutics Inc.
- I am a Consultant for AVROBIO, Inc.
- I am a member of the Cystinosis Research Foundation Scientific Review Board and Board of Trustees

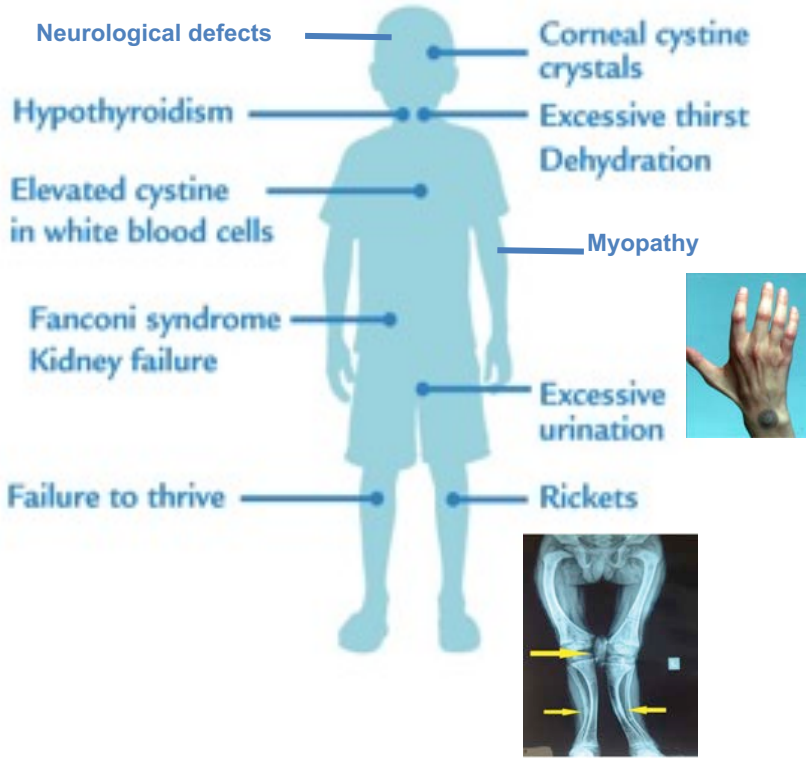
CYSTINOSIS, A LYSOSOMAL STORAGE DISORDER

- Autosomal recessive
- Incidence 1/100,000 – 1/200,000

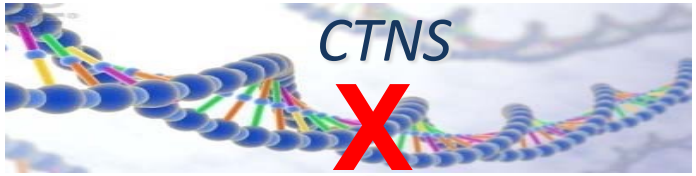




Multisystemic degenerative disease



CURRENT TREATMENT FOR CYSTINOSIS



Gene therapy

lysosomes
Cystine

cytoplasm
Cysteine

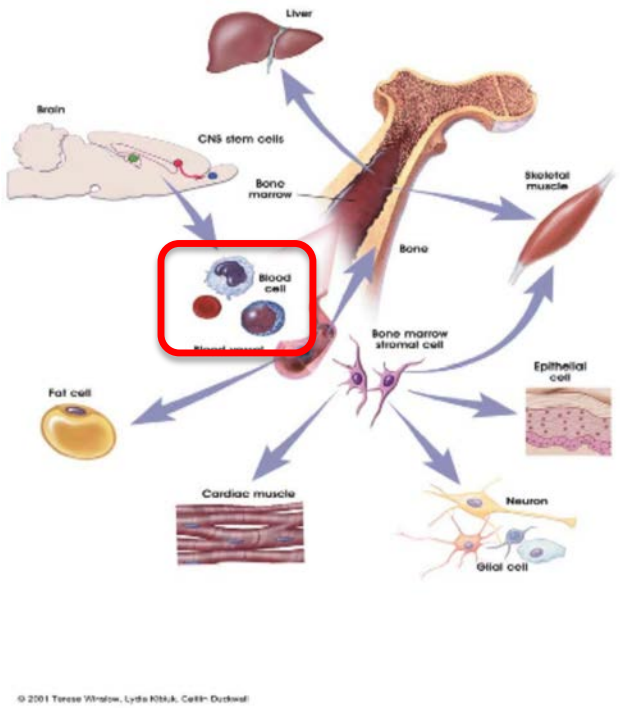
Cysteamine

Substrate reduction therapy

Cystinosis

Supportive therapy

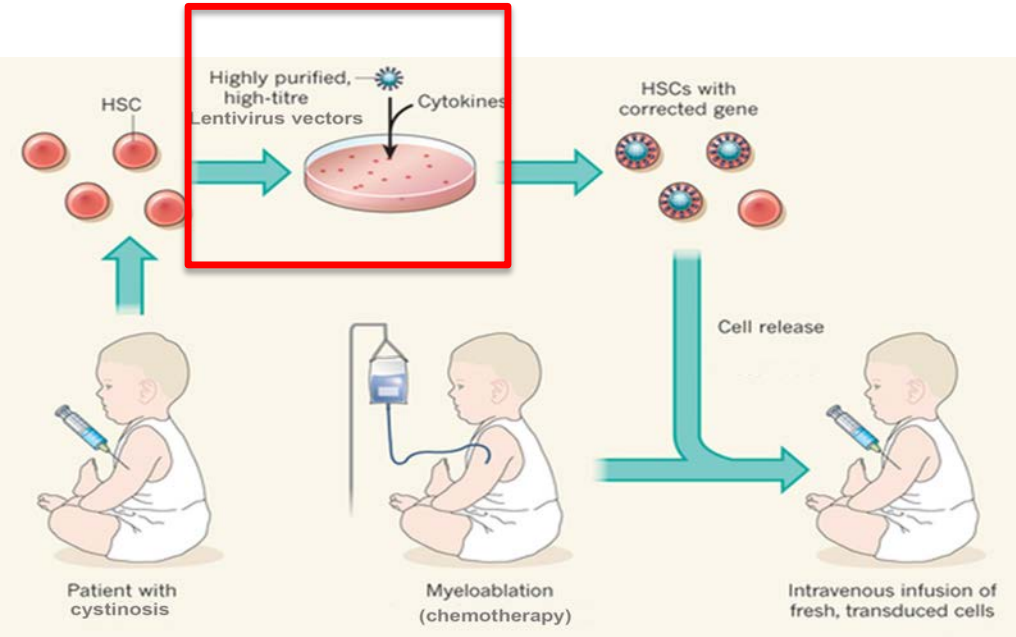
Adult bone marrow stem cells



- **Adult bone marrow stem cells**
  - Pluripotent
  - Safe
  - Currently used in clinical applications

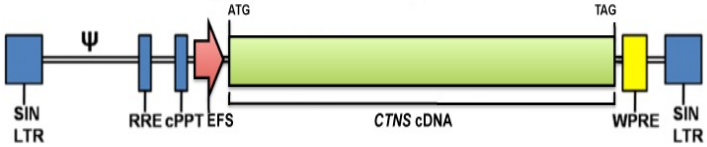
- **Three types of BMSC:**
  - Whole bone marrow cells (BMC)
  - Hematopoietic stem cells (HSC)
  - Mesenchymal stem cells (MSC)

CLINICAL TRANSLATION: AUTOLOGOUS GENE-MODIFIED HSC TRANSPLANTATION



Adapted from Leboulch, Nature 2013

CCL-EFS-CTNS-WPRE

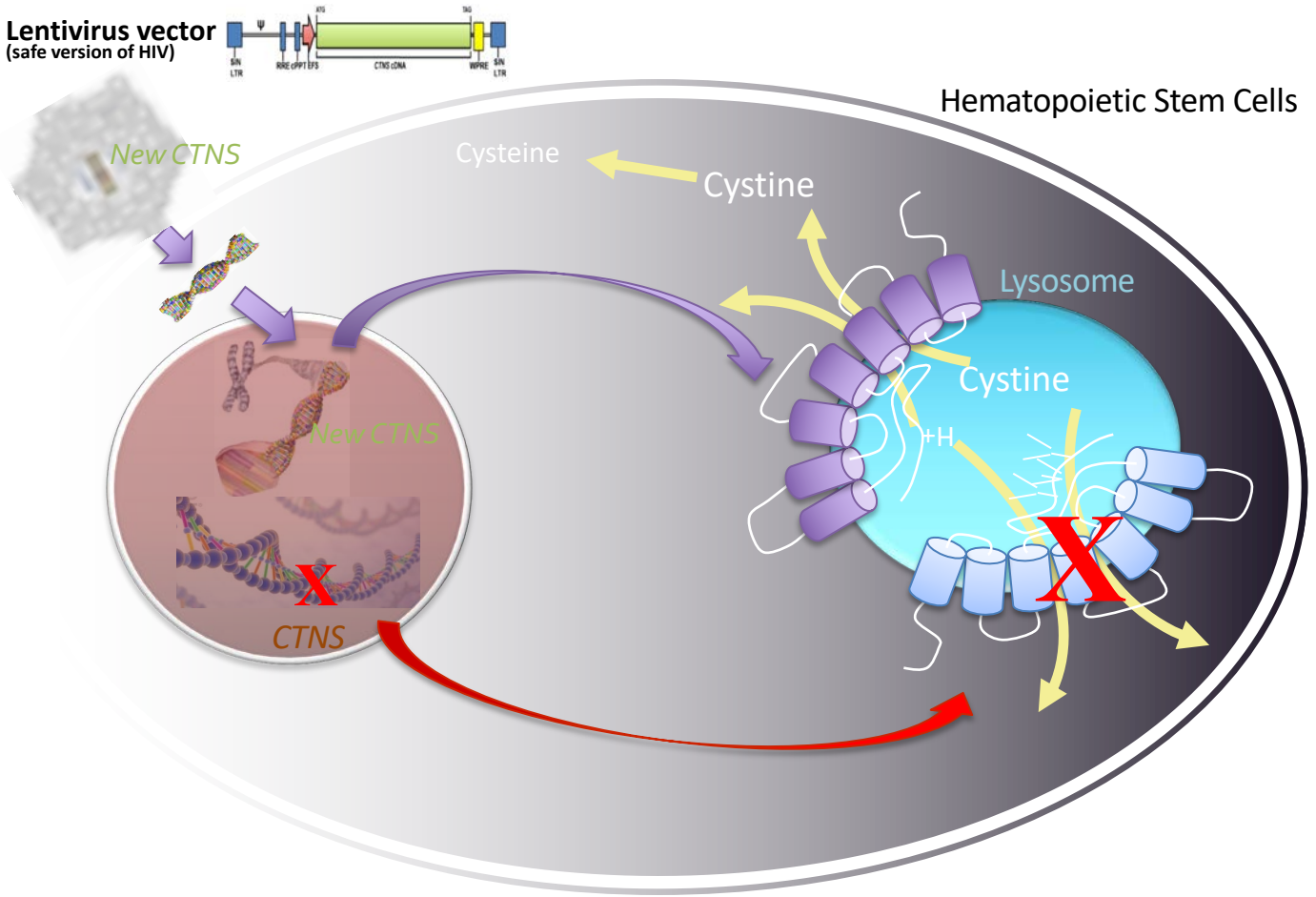


Lentivirus vector (engineered version of HIV)

Provided by Dr. Donald Kohn (UCLA)

Drug Product: CD34+ HSCs from patients, *ex vivo* gene-corrected using pCCL-CTNS

Ex vivo gene modification of the autologous stem cells



AUTOLOGOUS STEM CELL GENE THERAPY CLINICAL TRIAL FOR CYSTINOSIS

Trial started on July 8th, 2019 at UC San Diego Health Center
ClinicalTrials.gov Identifier # NCT03897361

UC San Diego Health

Study Design: One arm, open label, single treatment safety and efficacy study - **6 patients**

- **Primary Endpoints**
  - To assess the clinical tolerability and safety of treatment with CTNS-RD-04;
- **Secondary Endpoints**; To evaluate the impact of treatment with CTNS-RD-04 on:
  - To assess the effect of treatment with CTNS-RD-04 on white blood cell cystine levels
  - Clinical outcomes (especially kidney, eye and endocrine function)
  - Cystine level in tissues (rectal and skin biopsies)
  - Cystine crystal density (skin and eye)

Inclusion Criteria: 6 patients (3 cohorts of 2 patients)

- Cohort 1 and 2: Male or female subject is ≥ 18 years of age.
- Cohort 3: Male or female subject is ≥ 14 years of age.

- Subject is diagnosed with infantile cystinosis.
- Subject is free of acute illness.
- Subject is at least one-year status post-kidney transplant.
- Subject has adequate organ function.
- Subject is willing and able to comply with the study restrictions and requirements.
- Subject is willing to provide written informed consent prior to participation in the study.

THE CYSTINOSIS STEM CELL AND GENE THERAPY CONSORTIUM

Stephanie Cherqui, Ph.D - Hematopoietic Stem Cell Gene Therapy, UCSD – Principal Investigator

Bruce Barshop, M.D., Ph.D – Director of the UCSD Biochemical Genetics lab – Principal Investigator

Edward D. Ball, M.D – Director of Bone Marrow Transplantation at UCSD – Principal Investigator

Natalie Afshari, M.D – Ophthalmology, UCSD

Nadine Benador, M.D – Nephrology, UCSD

Anna DiNardo, M.D – Dermatology, UCSD

Magdalene Dohil, M.D – Dermatology, UCSD

Ranjan Dohil, M.D – Gastroenterology, UCSD

Robert Mak, M.D – Nephrology/Muscle, UCSD

Susan Phillips, M.D – Endocrinology, UCSD

Kathleen Rickert, M.D – Orthopedy, UCSD

Doris A. Trauner, M.D – Neurology, UCSD

Donald B. Kohn, M.D – Hematopoietic Stem Cell Gene Therapy, UCLA

Paul Grimm, M.D – Nephrology, Stanford

Nancy Stack – Director of the Cystinosis Research Foundation

CLINICAL PROCESS

UC San Diego Health

1- Inform Consent and Screening (2 days)

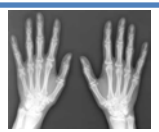
2- Baseline evaluation (8-9 days)

Kidney function
Blood, 24h urine
Iohexol clearance

Dr. Nadine Benador,
Dr. Robert Mak

Eye exam
Corneal confocal microscopy
Angiography
Electroretinogram
Optical Coherence Tomography

Dr. Natalie Afshari
Dr. Eric Nudleman

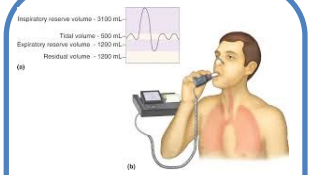


Muscle function, bone density
Walk test
Grip strength
X-ray absorptiometry (DEXA)

Dr. Robert Mak
Dr. Kathleen Rickert

Neurological function
Quality of Life
Neurological exam
Questionnaires

Dr. Doris Trauner

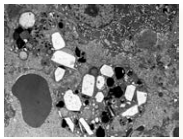


Respiration capacity
Spirometry

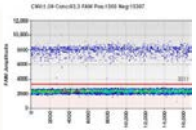
Endocrine function
Thyroid hormones
Fasting glucose
Reproductive hormones

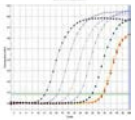
Rectal Biopsies

Dr. Ranjan Dohil

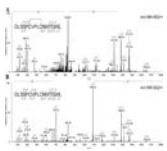


Histology to quantify cystine crystals



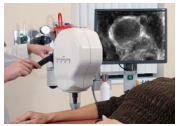


Vector Copy Number
CTNS expression



Cystine measures in blood and tissue

Dr. Bruce Barshop



In vivo confocal microscopy
Skin cystine crystal quantification

Dr. Magdalene Dohil

Patients stop oral cysteamine 2 weeks prior to drug product infusion and cysteamine eye drops 1-month post-infusion

PATIENTS' CELL MANUFACTURING AND TRANSPLANTATION

UC San Diego Health

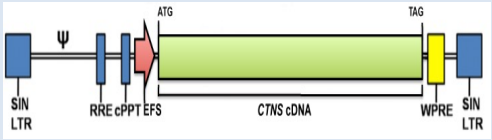
1- G-CSF/plerixaflor cell mobilization (4 days) and Apheresis

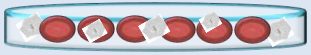
A back up apheresis product will be kept at UCSD

GMP Human Gene and Cell Therapy
Dr. Donald Kohn

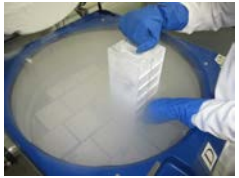
UCLA

CCL-EFS-CTNS-WPRE lentiviral vector



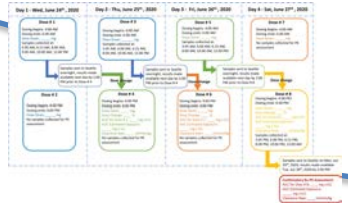


2- CD34⁺ cell isolation and transduction (3 days)



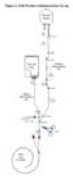
3- Cell characterization (UCSD/UCLA; 30-60 days)

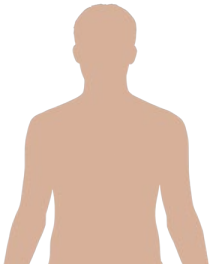
4- Gene-modified stem cells shipped back to UCSD as a cryopreserved product



5- Busulfan conditioning (4 days)
Targeted Area Under the Curve (AUC) - 90 mg x h/L

6- Infusion





Adult with cystinosis

Drug Product: CD34+ HSCs from patients, *ex vivo* gene-augmented using pCCL-CTNS or pCDY.EFS.CTNS.T260I – **CTNS-RD-04**

TRANSPLANTED PATIENTS AND MANUFACTURING PRODUCTS

	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4
Age of symptom onset/diagnosis	0 year / 8 months	0 year / 6 months	4 years	6 years
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**
Gender	Male	Male	Male	Male
Mutation	Allele 1: 57-kb deletion Allele 2: c.696dupC, p.Val233Argfs*63	Allele 1: 57-kb deletion Allele 2: c.473T>C, p.Leu158Pro	Allele 1: c.18_21del, p.Thr7Phefs*7 Allele 2: c.295_298del,p.Val99Ilefs*18	Allele 1: 57-kb deletion Allele 2: c.473T>C, p.Leu158Pro
Kidney transplant status and cysteamine dosing prior to CTNS-RD-04 dosing	• No kidney transplant; stage 3 (moderate CKD) renal failure • Cysteamine 1125 mg p.o. daily • Cysteamine drops 4-5x/day	• 2 renal transplants (1987 and 1999) • Cysteamine 1800 mg p.o. daily • Cysteamine drops 6x daily	• 1 renal transplant (2010) • Cysteamine 1200 mg p.o. daily • Cysteamine drops 5x daily	• 2 renal transplants (2008 and 2017) • Cysteamine 1800 mg p.o. daily • No Cysteamine drop in 2021
Manufactured CTNS-RD-04 product and Busulfan dose	• **7.88 x 10e6** $CD34^+$ cells/kg • Vector Copy Number: **2.07** • 94% viability • AUC Bu: 81.8 mg x h/L	• **5.07 x 10e6** $CD34^+$ cells/kg • Vector Copy Number: **1.27** • 91% viability • AUC Bu: 86.7 mg x h/L	• **9.59 x 10e6** $CD34^+$ cells/kg • Vector Copy Number: **1.59** • 95% viability • AUC Bu: 90 mg x h/L	• **3.63 x 10e6** $CD34^+$ cells/kg • Vector Copy Number: **0.59** • 90% viability • AUC Bu: 88.5 mg x h/L

Phase 1/2 Cystinosis Trial (4 patients)

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

Preliminary Safety Results

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

No SAE reported

Preliminary AEs reported (as of February 28th, 2022)

- N=40 for subject 1; N=22 for subject 2; N=5 for subject 3; N=24 for subject 4
- Majority of AEs are mild or moderate
- 1 severe AEs for subject 1
    - *Appendicitis* (resolved) – unrelated to study treatment or procedures
- AEs are generally consistent with myeloablative conditioning or underlying disease:

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

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

Post-treatment (not all events listed)

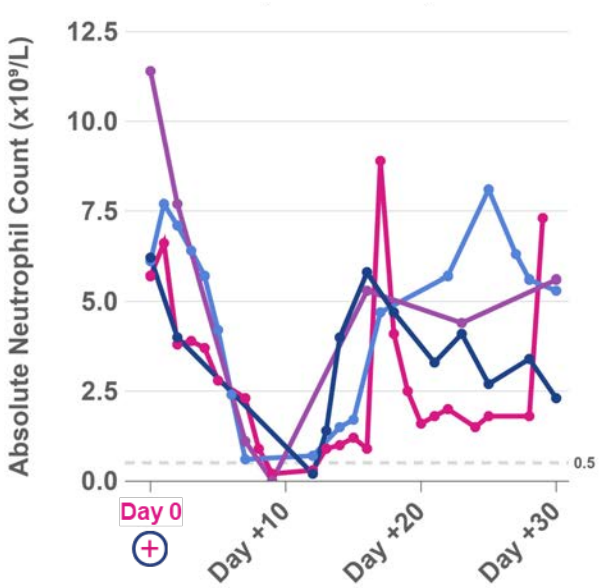
- Pancytopenia, deep vein thrombosis, Staphylococcus sepsis, Coronavirus infection, alopecia, rash, mucositis.
- Intermittent: diarrhea, vomiting, loss of appetite, epistaxis, blurry vision, febrile neutropenia, hypomagnesemia, and hypokalemia.

AE: Adverse Event; SAE: Serious Adverse Event

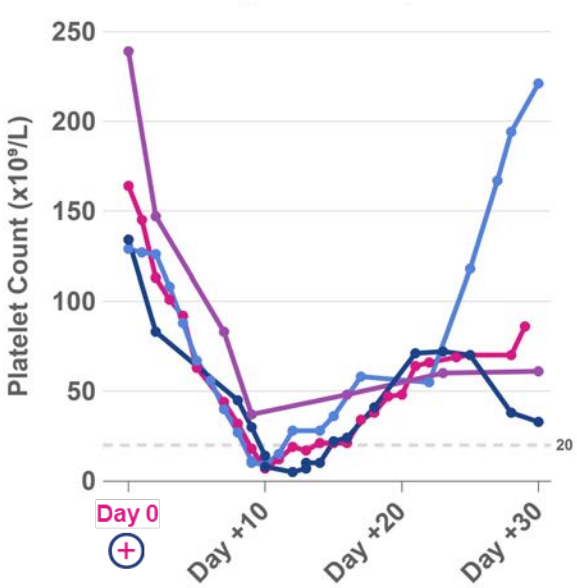
BLOOD COUNT

Busulfan is transiently myeloid depleting while sparing lymphocytes

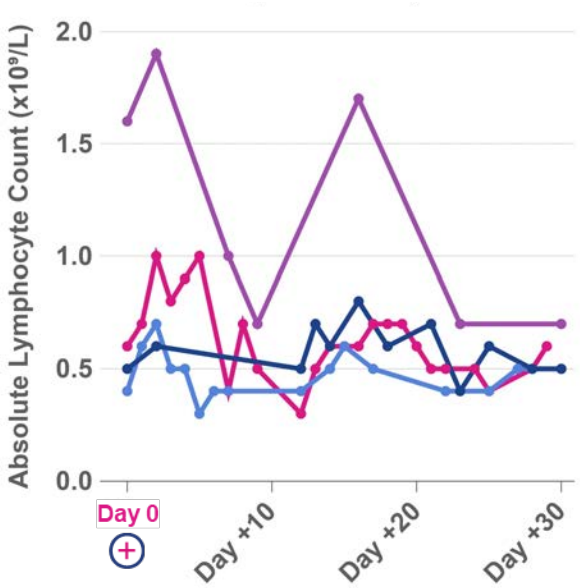
Absolute Neutrophil Count (ANC)



Platelet Count



Absolute Lymphocyte Count



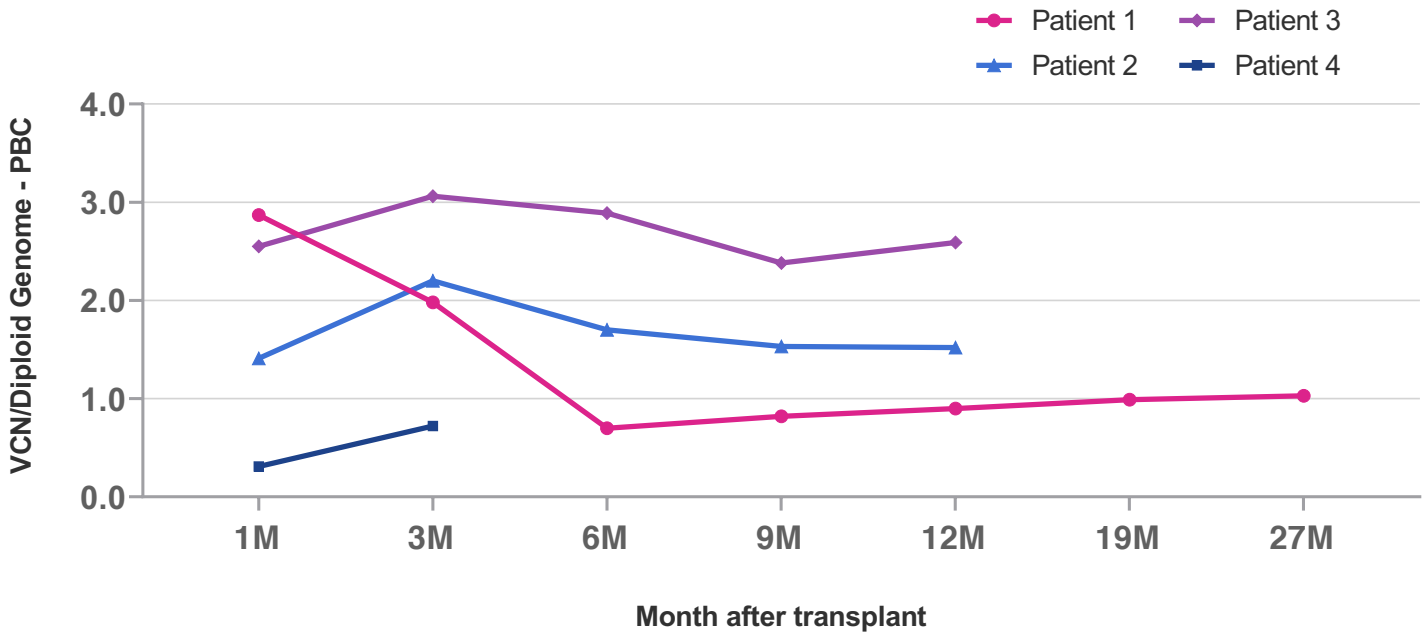
Patient 1 Patient 2 Patient 3 Patient 4

PRELIMINARY DATA

VECTOR COPY NUMBER (VCN)

Measured in the peripheral blood of patients at different time points

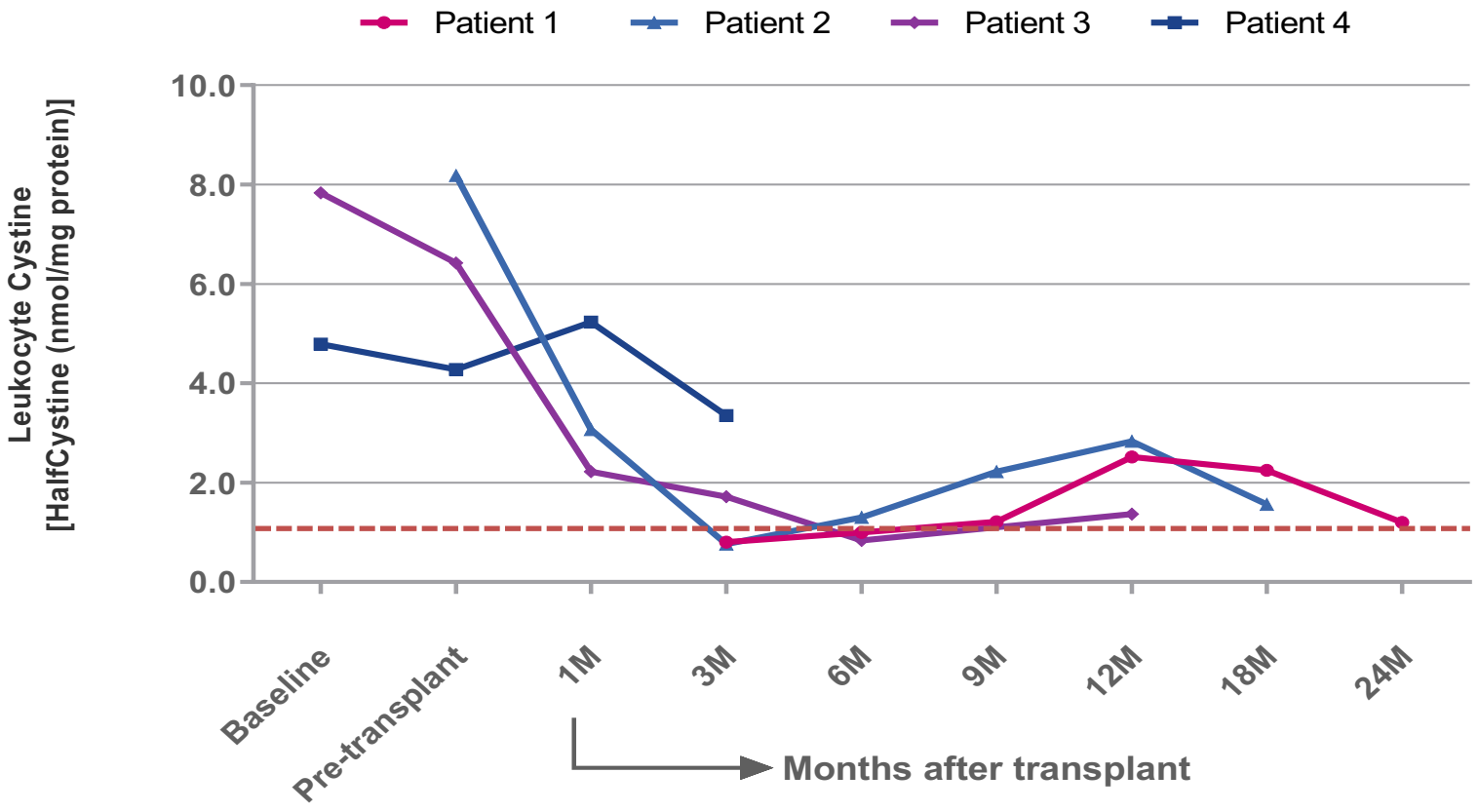
Drug Product (VCN/dg)	
Patient 1	2.1
Patient 2	1.3*
Patient 3	1.6
Patient 4	0.6



** From second apheresis*

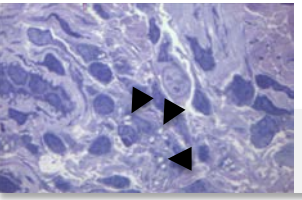
VCN: Vector Copy Number; PBCs: Peripheral Blood Cells; dg: Diploid Genome

LEUKOCYTE CYSTINE MEASURES



Note: For Patient 1, Leukocyte Cystine Quantification was initiated at approximately week 20

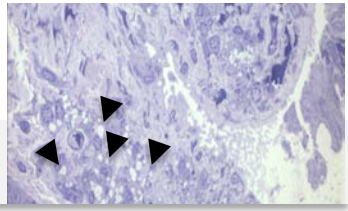
TISSUE CYSTINE CRYSTALS: BIOPSIES



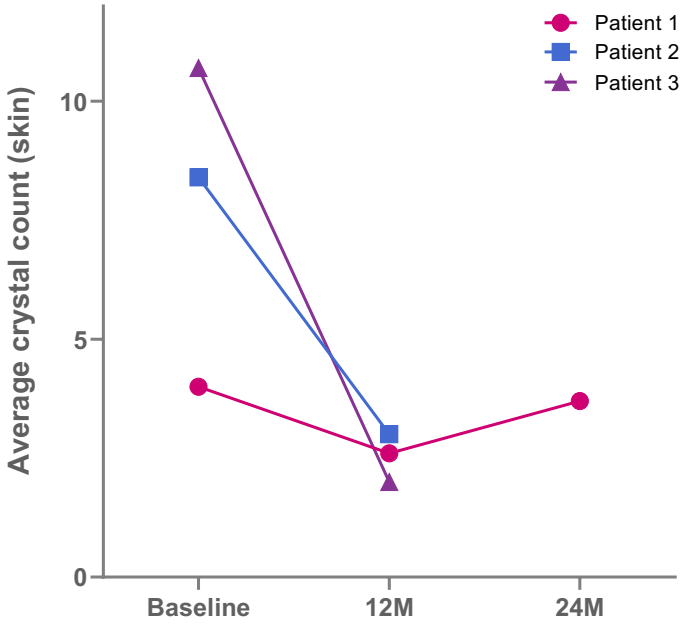
Skin biopsy image at Baseline - Patient 1

Average intracytoplasmic crystals per cell

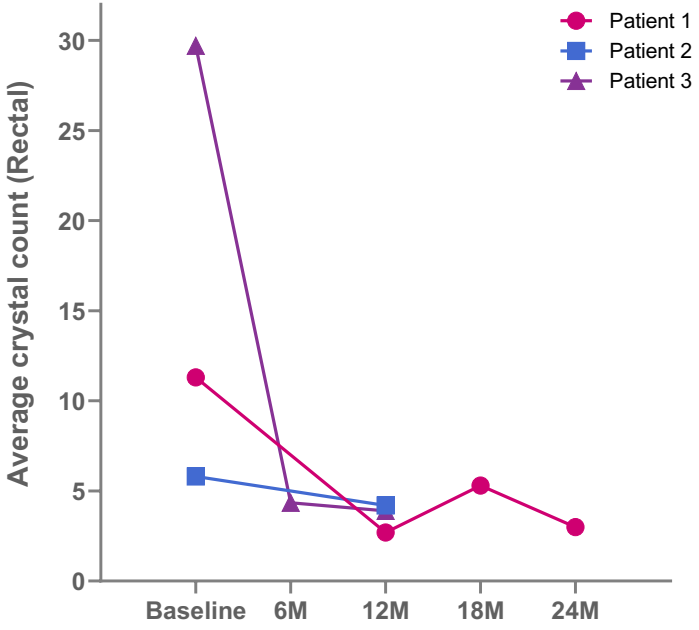
Rectal biopsy image at Baseline - Patient 1



Skin Biopsy

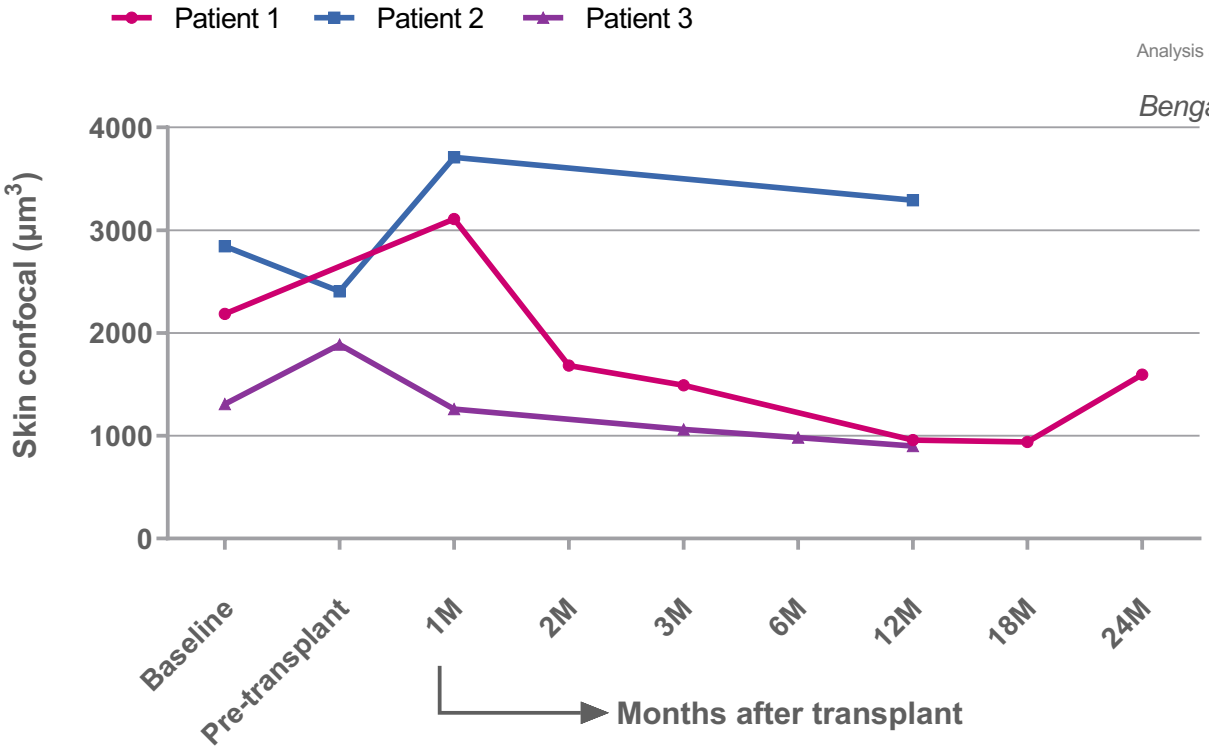


Rectal Biopsy

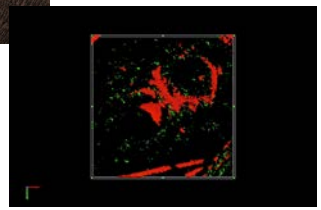


TISSUE CYSTINE CRYSTALS IN THE SKIN: CONFOCAL

Exploratory endpoint

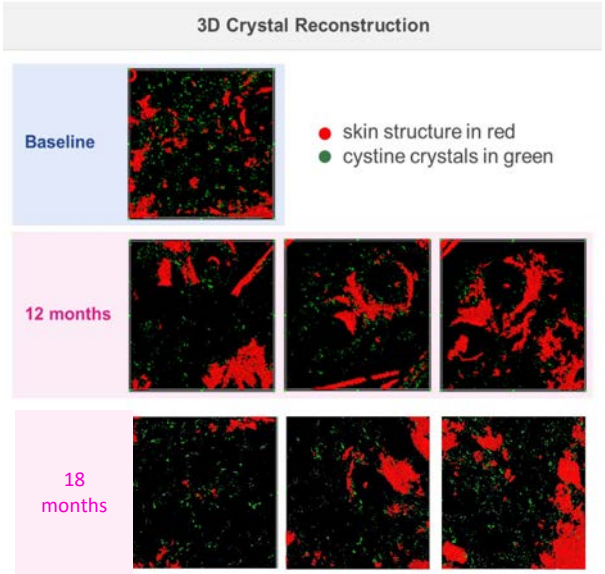


Caliber Vivascope® Skin Confocal microscope



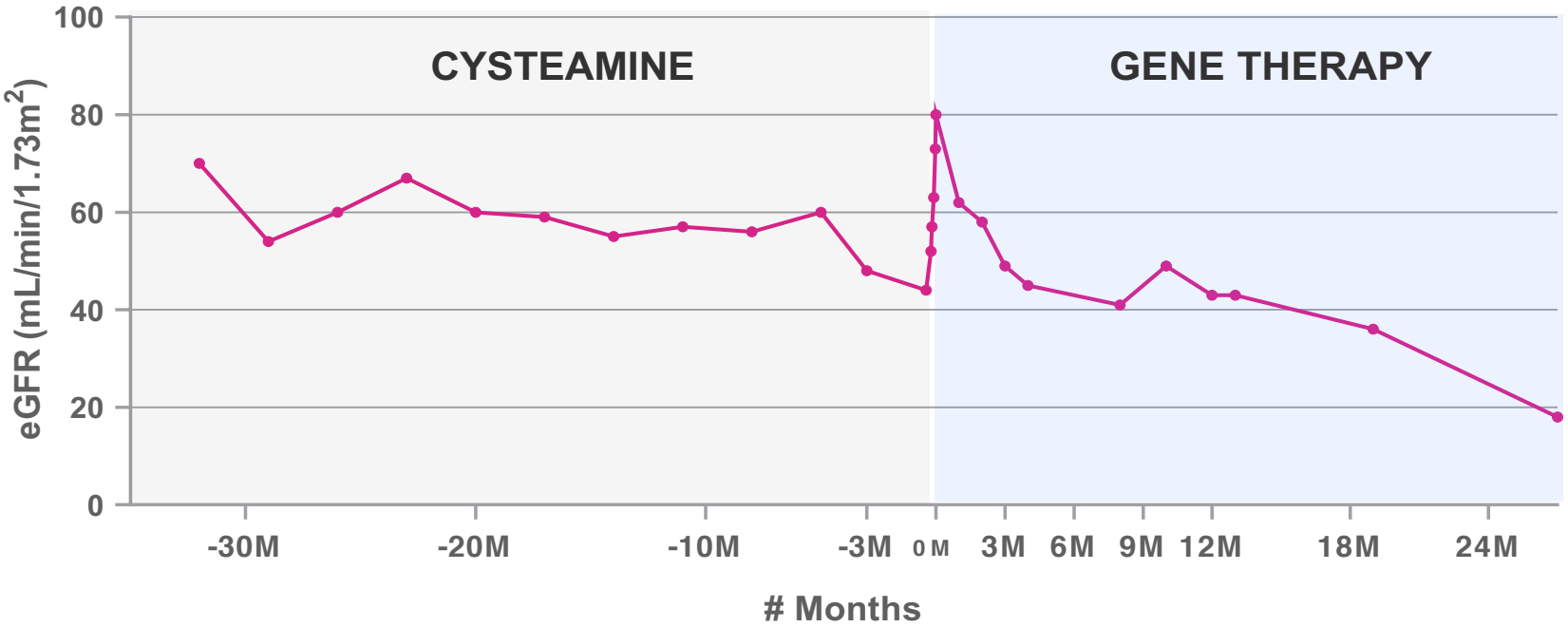
Analysis and quantification (3D Image-Pro software)

Bengali et al, PLOS ONE 2021



PATIENT 1: KIDNEY FUNCTION

Patient 1: Comparison of patient's natural history eGFR to eGFR post gene therapy

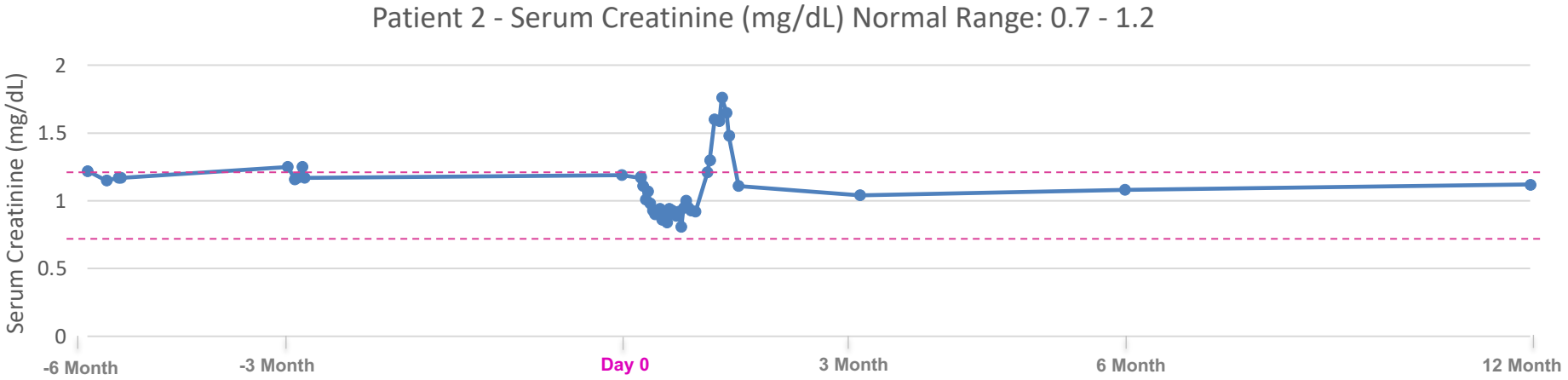


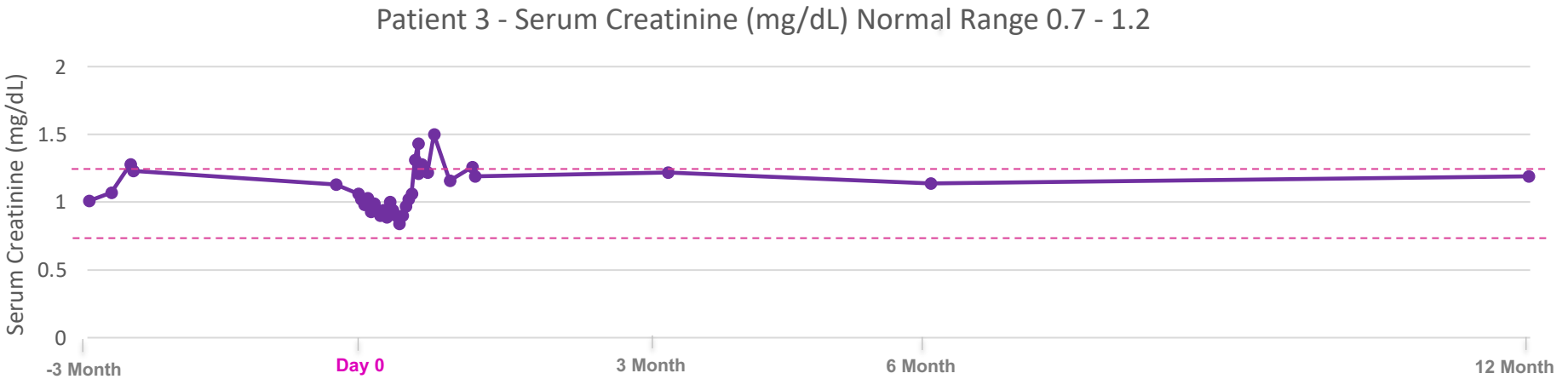
**Most of eGFR points represent an average of 2 to 8 eGFR value during the time period, except for Month 1 that represents an average of 29 eGFR values*

PRELIMINARY DATA

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

PATIENT 2 AND 3 – KIDNEY FUNCTION

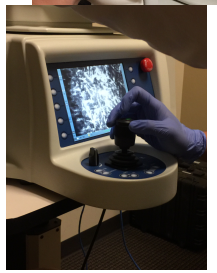




PRELIMINARY DATA

PATIENT 1 – TISSUE CYSTINE CRYSTALS IN THE CORNEA

Corneal confocal microscopy



Baseline IVCM Heldelberg images	7 months IVCM Heldelberg images	9 months IVCM Heldelberg images	12 months IVCM Heldelberg images	18 months IVCM Heldelberg images
174 µm, OD	175 µm, OD	176 µm, OD	176 µm, OD	176 µm, OD
331 µm, OD	331 µm, OD	317 µm, OD	331 µm, OD	331 µm, OD

Front of Cornea

Back of Cornea

CORNEAL CRYSTALS

Preliminary scoring performed by Dr. Hong Liang, *CNRS, Paris, France*

Eye layers	OD (right eye)		OS (left eye)	
	Baseline	12 months	Baseline	12 months
Anterior Stroma	4	3	4	1.86
Middle Stroma	4	3	4	1.71
Posterior Stroma	4	2.13	4	2

Score range: 1-5 where 1 is no photophobia and 5 is severe

Photophobia Grade (Patient reported)	
Pre-Conditioning	3
3 Months PT	Moderate
12 Months PT	1
18 Months PT	3
24 Months PT	1

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

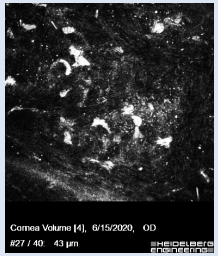
PATIENT 2 – TISSUE CYSTINE CRYSTALS IN THE CORNEA

Front of Cornea

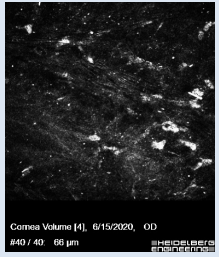
Back of Cornea

Baseline
IVCM Heidelberg images

43 µm, OD



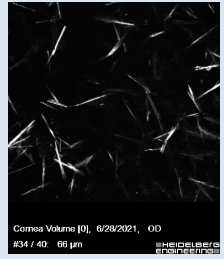
66 µm, OD



12 Months PT
IVCM Heidelberg images

43 µm, OD

66 µm, OD



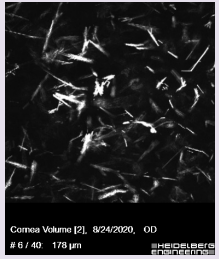
Photophobia Grade	
Baseline	2 or 3
12 Months PT	2

Score range: 1-5 where 1 is no photophobia and 5 is severe

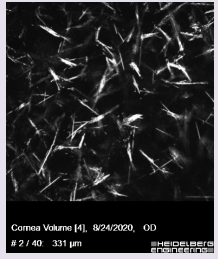
PATIENT 3 – TISSUE CYSTINE CRYSTALS IN THE CORNEA

Baseline
IVCM Heidelberg images

178 µm, OD

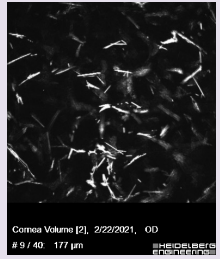


331 µm, OD

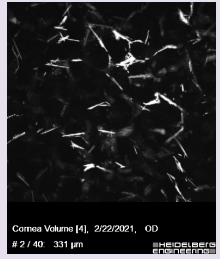


3 Months PT
IVCM Heidelberg images

177 µm, OD

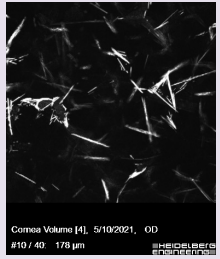


331 µm, OD

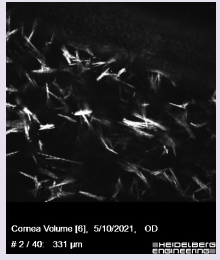


6 Months PT
IVCM Heidelberg images

178 µm, OD



331 µm, OD



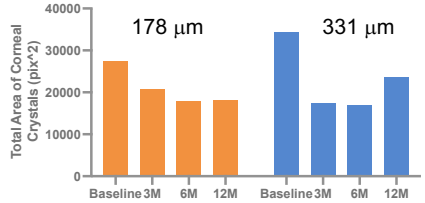
12 Months PT
IVCM Heidelberg images

178 µm, OD

331 µm, OD

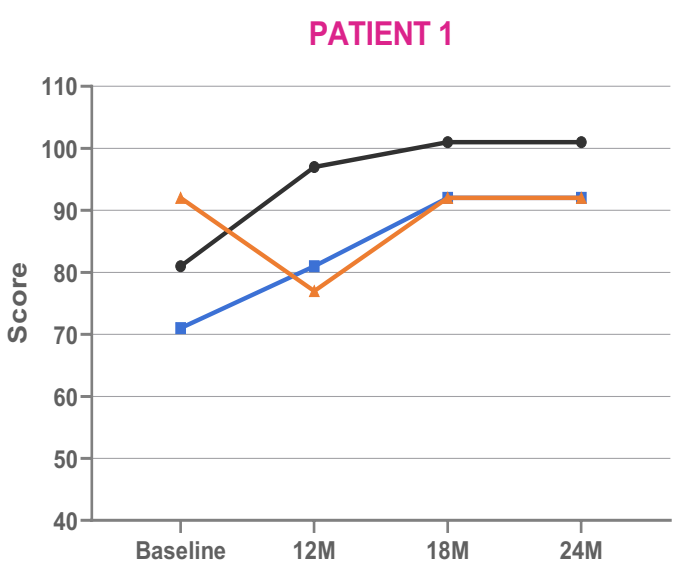
Photophobia Grade	
Baseline	2
3 Months PT	2.5
6 Months PT	3
12 Months PT	2

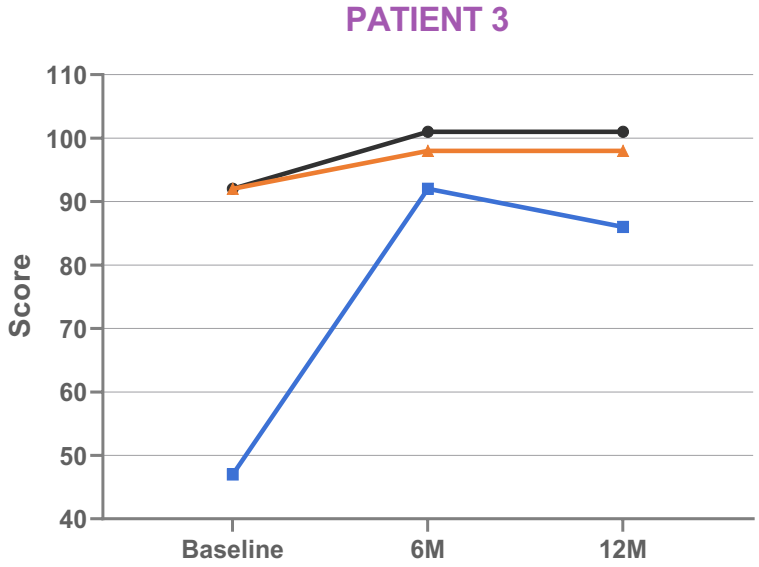
PATIENT 3



NEUROCOGNITIVE ASSESSEMENTS

Dr. Doris Trauner





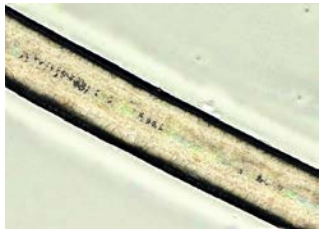
Beery Test of Visual Motor Integration (VMI)

Motor coordination score

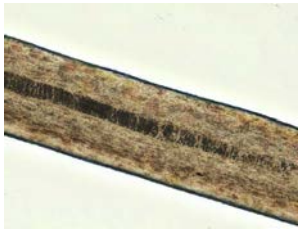
Visual perception score

EXPLORATORY ENDPOINT: HAIR, SKIN AND EYE COLOR

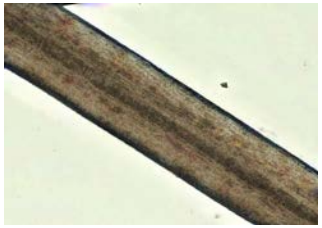
12 Months PT



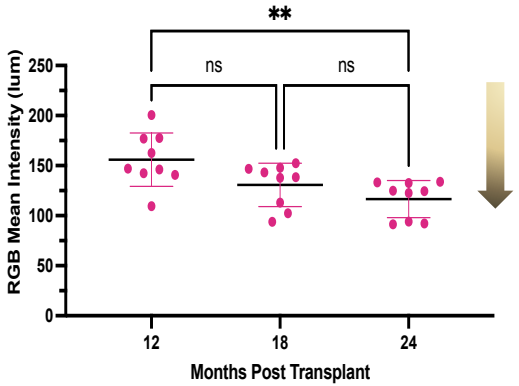
18 Months PT



24 Months PT

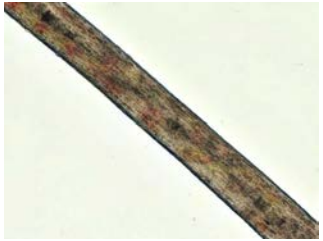


CT.001 Hair color – RGB intensity



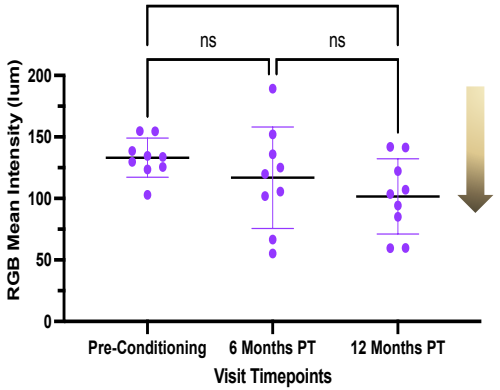
Baseline

6 Months PT



12 Months PT

CT.005 Hair color – RGB intensity



PATIENTS 1- 4

All patients continue to be oral cysteamine-independent

	PATIENT	MONTHS OFF CYSTEAMINE PILLS AND EYE DROPS POST CTNS-RD-04 INFUSION	CURRENT STATUS
cysteamine pills	PATIENT 1	29	OFF
	PATIENT 2	21	OFF
	PATIENT 3	16	OFF
	PATIENT 4	4	OFF
cysteamine eye drops	PATIENT 1	29	OFF
	PATIENT 2	13	ON (patient elected to re-start July 2021)
	PATIENT 3	16	OFF
	PATIENT 4	Was not on cysteamine eye drops prior to infusion	OFF

Note: All 3 subjects remain off cysteamine pills. Subjects 1 and 3 remain off cysteamine eye drops. Subject 2 elected to re-start cysteamine eyedrops
Subjects 2 and 3 stopped cysteamine eye drops 1-month post-transplant (per protocol).
Subject 1 stopped cysteamine eye drops prior to baseline.
Data as of March 2, 2022

CYSTINOSIS RESEARCH FOUNDATION
NATALIE'S WISH

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