



UNIVERSITY *of* CALIFORNIA, SAN DIEGO  
SCHOOL OF MEDICINE

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

---

Stephanie Cherqui, Ph.D  
Associate Professor  
Department of Pediatrics

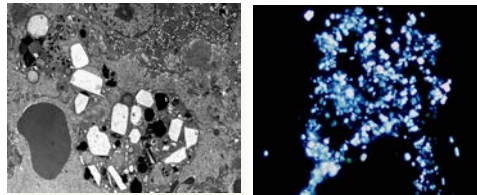
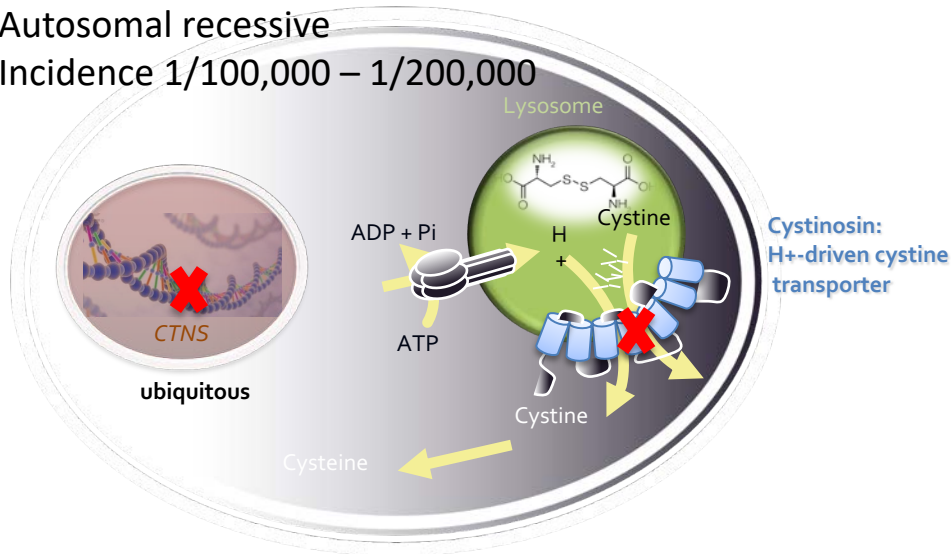


## DISCLOSURE

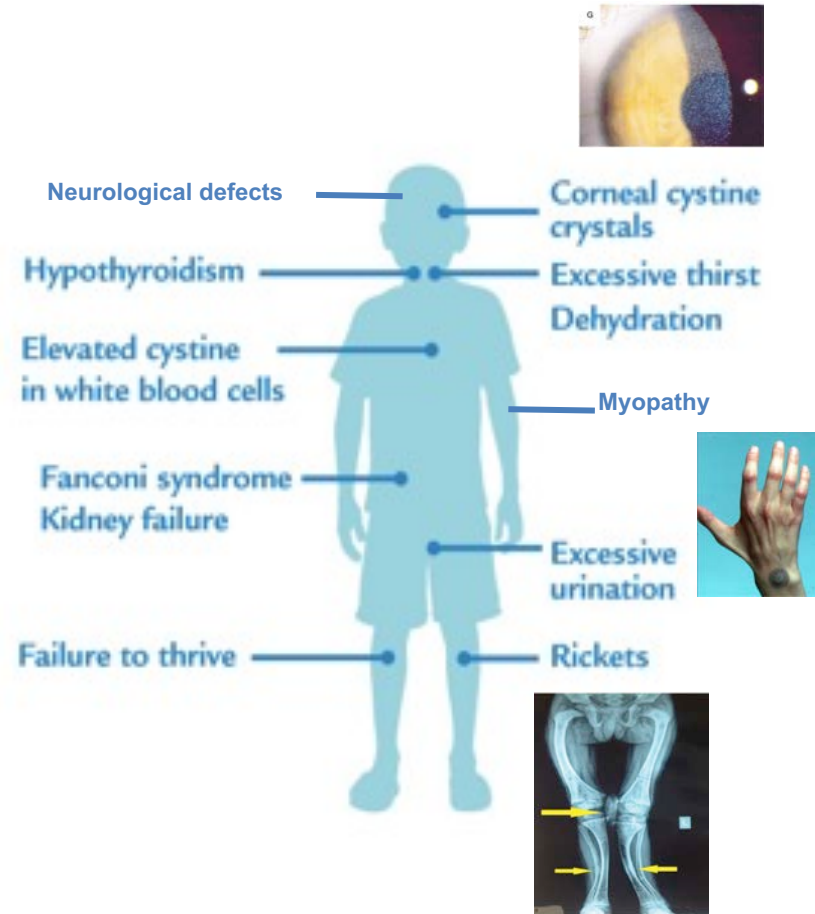
- I am cofounder, shareholder and a member of both the scientific board and board of directors of Papillon Therapeutics Inc.
- I am a Consultant for AVROBIO, Inc.
- I am a member of the Cystinosis Research Foundation Scientific Review Board and Board of Trustees

# CYSTINOSIS, A LYSOSOMAL STORAGE DISORDER

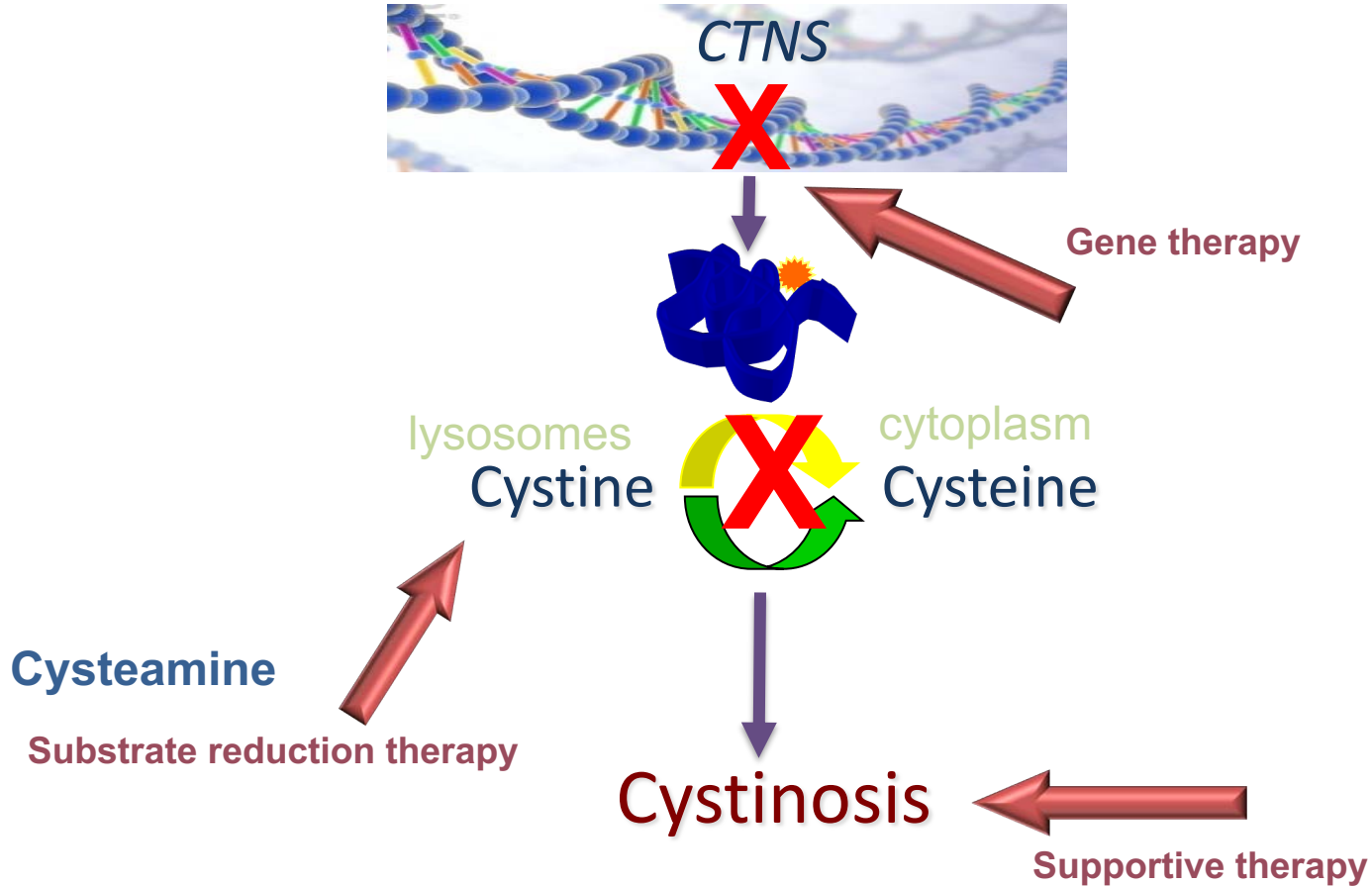
- Autosomal recessive
- Incidence 1/100,000 – 1/200,000



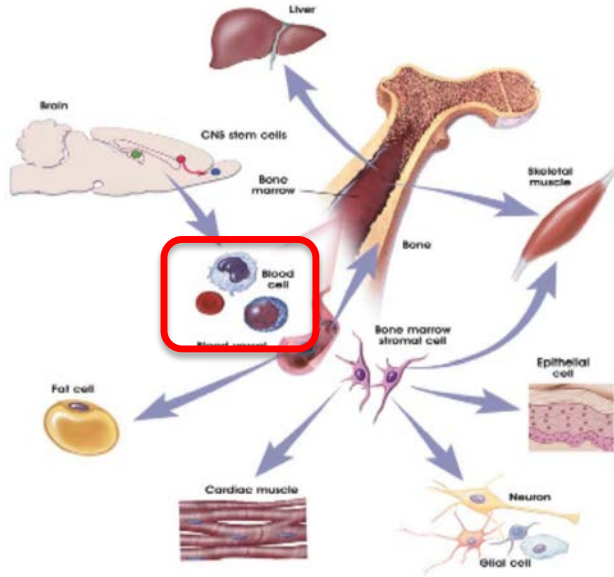
**Multisystemic degenerative disease**



# CURRENT TREATMENT FOR CYSTINOSIS



# Adult bone marrow stem cells



© 2001 Teresa Whitrow, Lydia Nikitk, Cell® Dordrecht

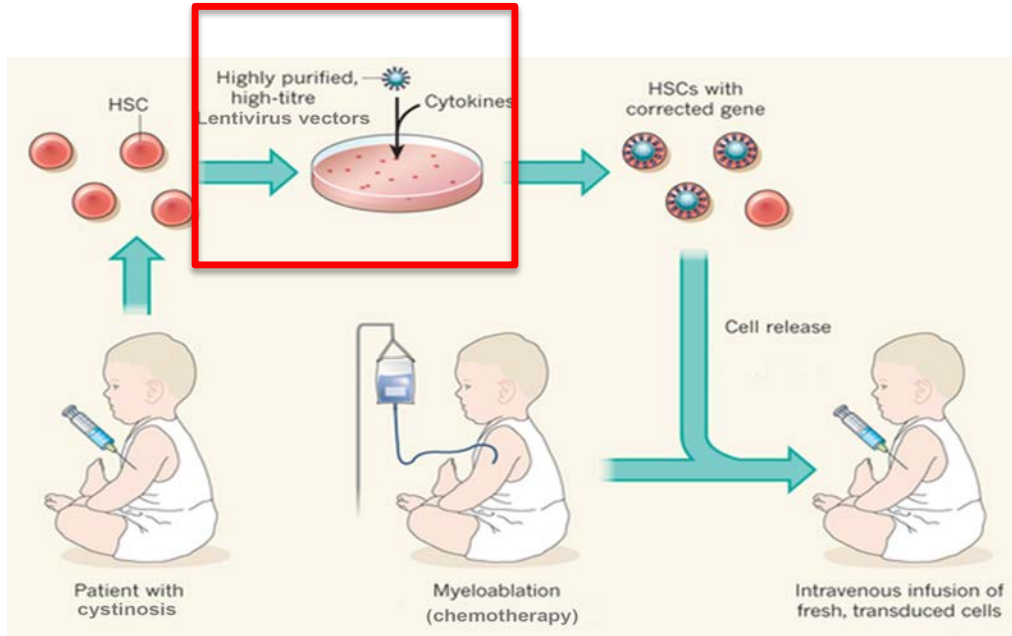
## ➤ Adult bone marrow stem cells

- Pluripotent
- Safe
- Currently used in clinical applications

## ➤ Three types of BMSC:

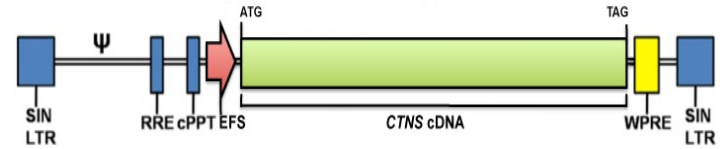
- Whole bone marrow cells (BMC)
- Hematopoietic stem cells (HSC)
- Mesenchymal stem cells (MSC)

# CLINICAL TRANSLATION: AUTOLOGOUS GENE-MODIFIED HSC TRANSPLANTATION



Adapted from Leboulch, *Nature* 2013

CCL-EFS-CTNS-WPRE



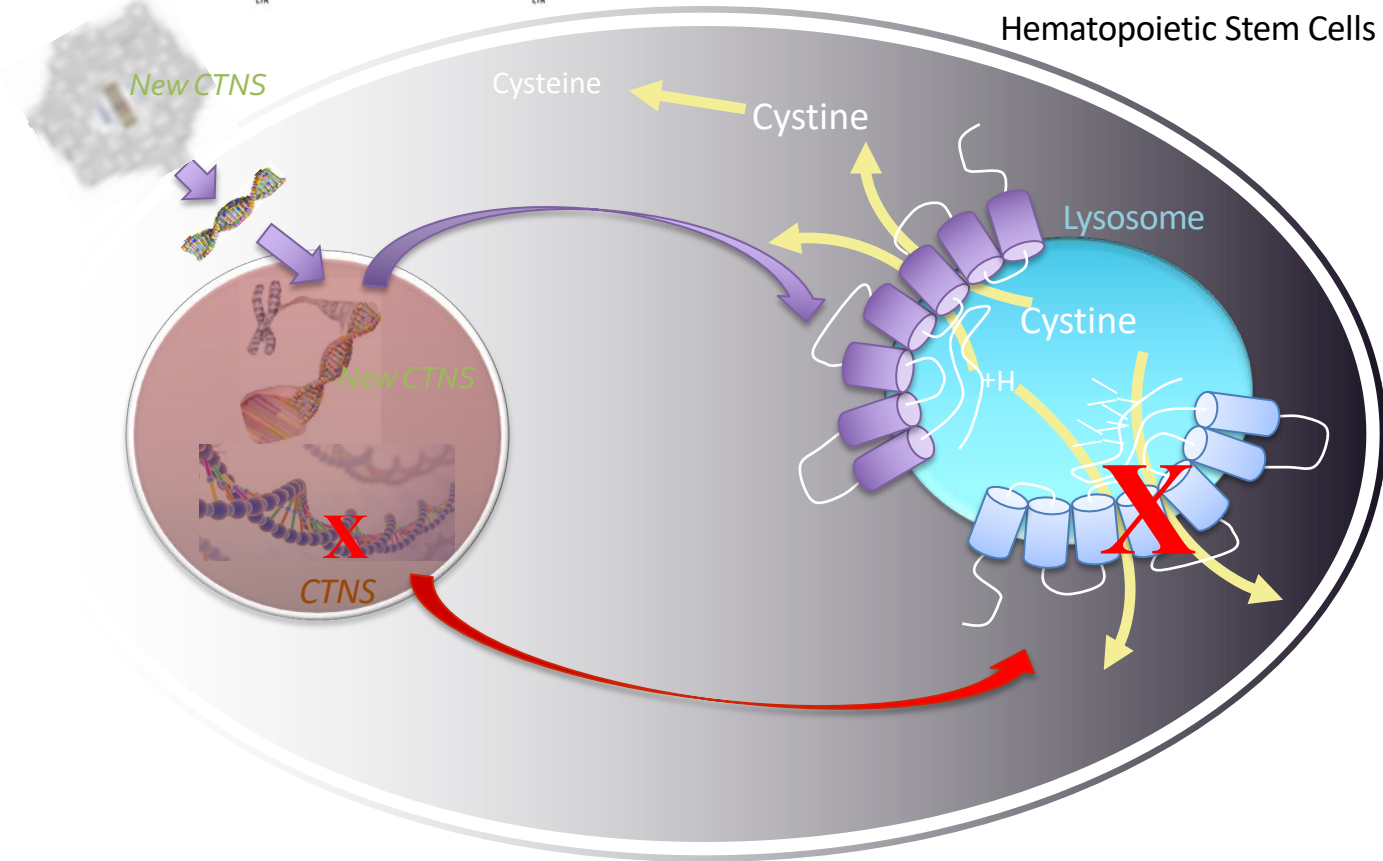
Lentivirus vector (engineered version of HIV)

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

Lentivirus vector  
(safe version of HIV)



# 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

**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  $\geq 18$  years of age.
- Cohort 3: Male or female subject is  $\geq 14$  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.



UC San Diego Health



## 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



**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)

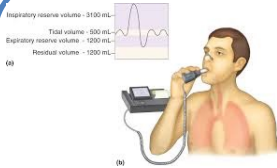
**Dr. Robert Mak  
Dr. Kathleen Rickert**



**Neurological function**

**Quality of Life**  
Neurological exam  
Questionnaires

**Dr. Doris Trauner**



**Respiration capacity**  
Spirometry

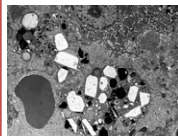


**Endocrine function**

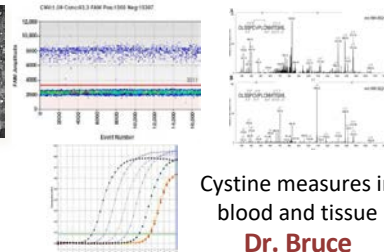
Thyroid hormones  
Fasting glucose  
Reproductive hormones

**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

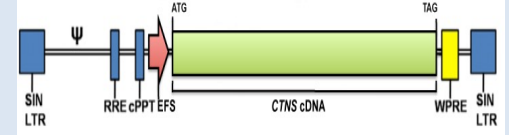
**Dr. Magdalene  
Dohil**

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



GMP Human Gene and Cell Therapy  
Dr. Donald Kohn

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

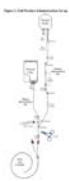
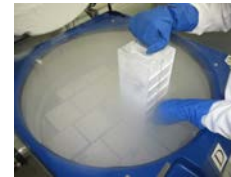
1- G-CSF/plerixaflor cell mobilization (4 days) and Apheresis

A back up apheresis product will be kept at UCSD

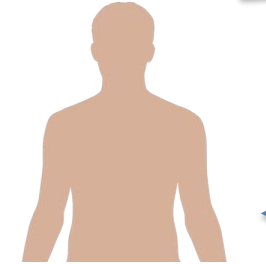


6- Infusion

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



UC San Diego Health



Adult with cystinosis



# TRANSPLANTED PATIENTS AND MANUFACTURING PRODUCTS

	PATIENT 1	PATIENT 2	PATIENT 3	PATIENT 4
<b>Age of symptom onset/diagnosis</b>	0 year / 8 months	0 year / 6 months	4 years	6 years
<b>Age dosed with CTNS-RD-04</b>	20 years Infused October 2019	46 years Infused June 2020	22 years Infused November 2020	33 years Infused November 2021
<b>Gender</b>	Male	Male	Male	Male
<b>Mutation</b>	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
<b>Kidney transplant status and cysteamine dosing prior to CTNS-RD-04 dosing</b>	<ul style="list-style-type: none"> <li>No kidney transplant; stage 3 (moderate CKD) renal failure</li> <li>Cysteamine 1125 mg p.o. daily</li> <li>Cysteamine drops 4-5x/day</li> </ul>	<ul style="list-style-type: none"> <li>2 renal transplants (1987 and 1999)</li> <li>Cysteamine 1800 mg p.o. daily</li> <li>Cysteamine drops 6x daily</li> </ul>	<ul style="list-style-type: none"> <li>1 renal transplant (2010)</li> <li>Cysteamine 1200 mg p.o. daily</li> <li>Cysteamine drops 5x daily</li> </ul>	<ul style="list-style-type: none"> <li>2 renal transplants (2008 and 2017)</li> <li>Cysteamine 1800 mg p.o. daily</li> <li>No Cysteamine drop in 2021</li> </ul>
<b>Manufactured CTNS-RD-04 product and Busulfan dose</b>	<ul style="list-style-type: none"> <li><b>7.88 x 10e6</b> CD34<sup>+</sup> cells/kg</li> <li>Vector Copy Number: <b>2.07</b></li> <li>94% viability</li> <li>AUC Bu: 81.8 mg x h/L</li> </ul>	<ul style="list-style-type: none"> <li><b>5.07 x 10e6</b> CD34<sup>+</sup> cells/kg</li> <li>Vector Copy Number: <b>1.27</b></li> <li>91% viability</li> <li>AUC Bu: 86.7 mg x h/L</li> </ul>	<ul style="list-style-type: none"> <li><b>9.59 x 10e6</b> CD34<sup>+</sup> cells/kg</li> <li>Vector Copy Number: <b>1.59</b></li> <li>95% viability</li> <li>AUC Bu: 90 mg x h/L</li> </ul>	<ul style="list-style-type: none"> <li><b>3.63 x 10e6</b> CD34<sup>+</sup> cells/kg</li> <li>Vector Copy Number: <b>0.59</b></li> <li>90% viability</li> <li>AUC Bu: 88.5 mg x h/L</li> </ul>

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 28<sup>th</sup>, 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.

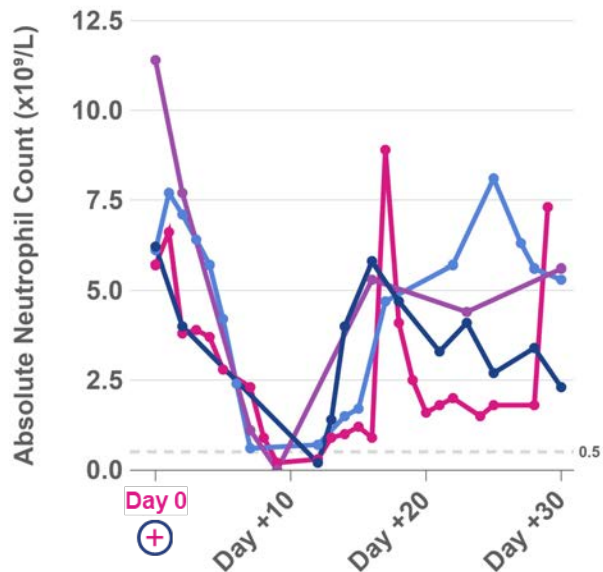
#### Post-treatment (not all events listed)

- 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.

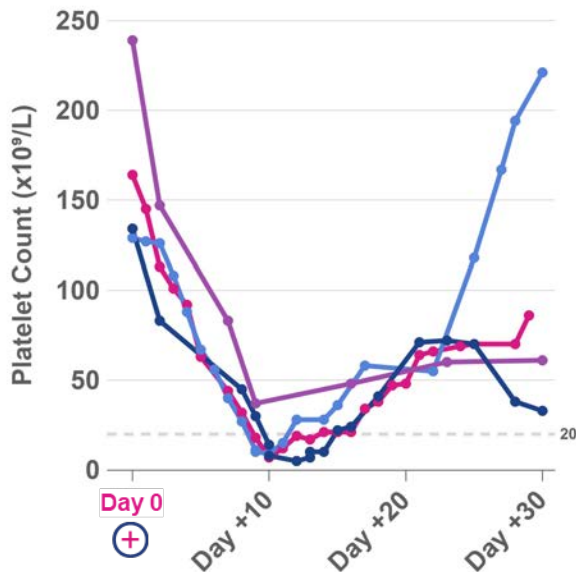
# BLOOD COUNT

Busulfan is transiently myeloid depleting while sparing lymphocytes

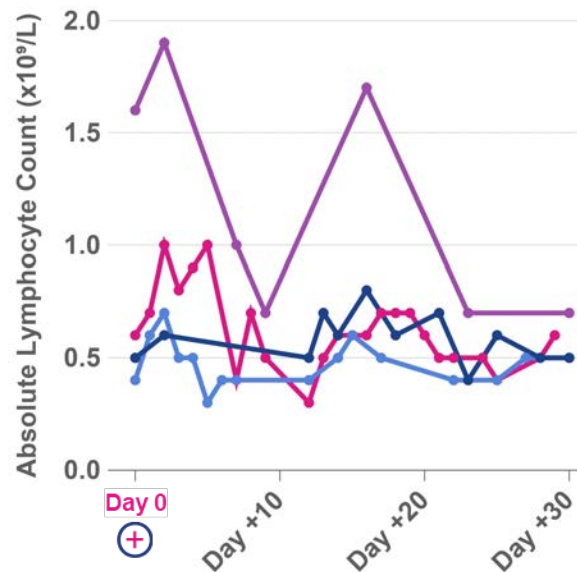
### Absolute Neutrophil Count (ANC)



### Platelet Count



### Absolute Lymphocyte Count

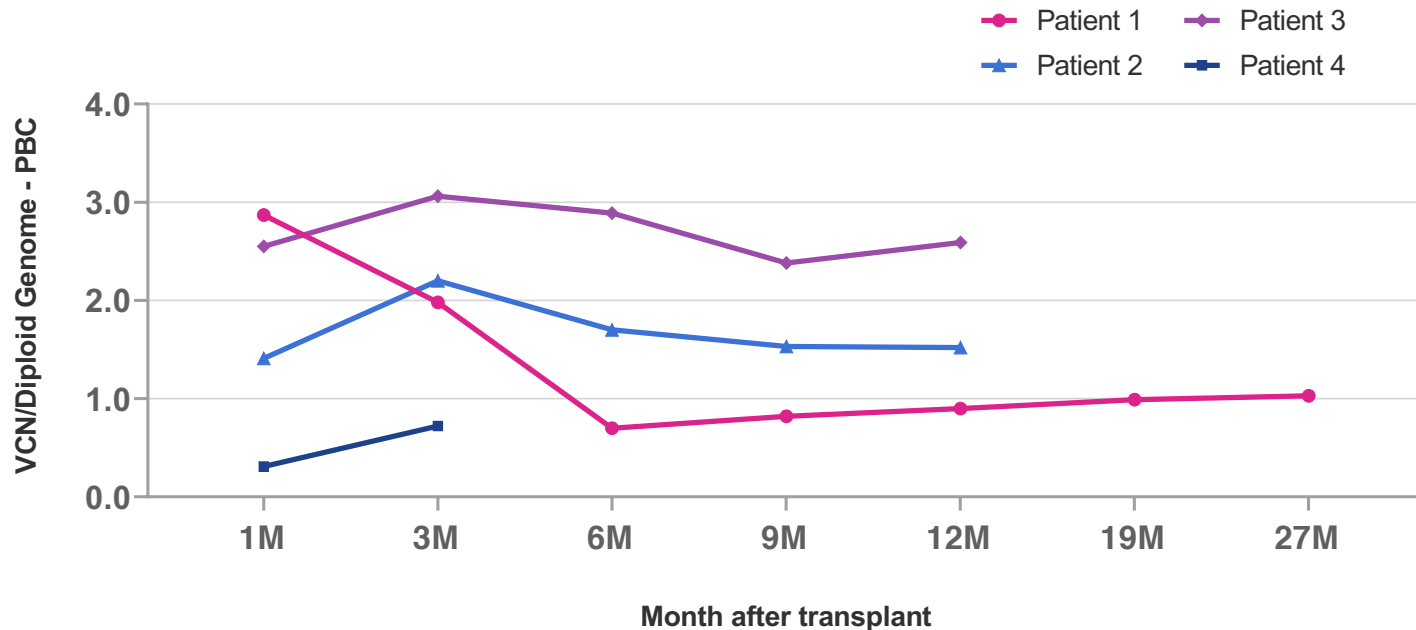


— Patient 1 — Patient 2 — Patient 3 — Patient 4

## VECTOR COPY NUMBER (VCN)

Measured in the peripheral blood of patients at different time points

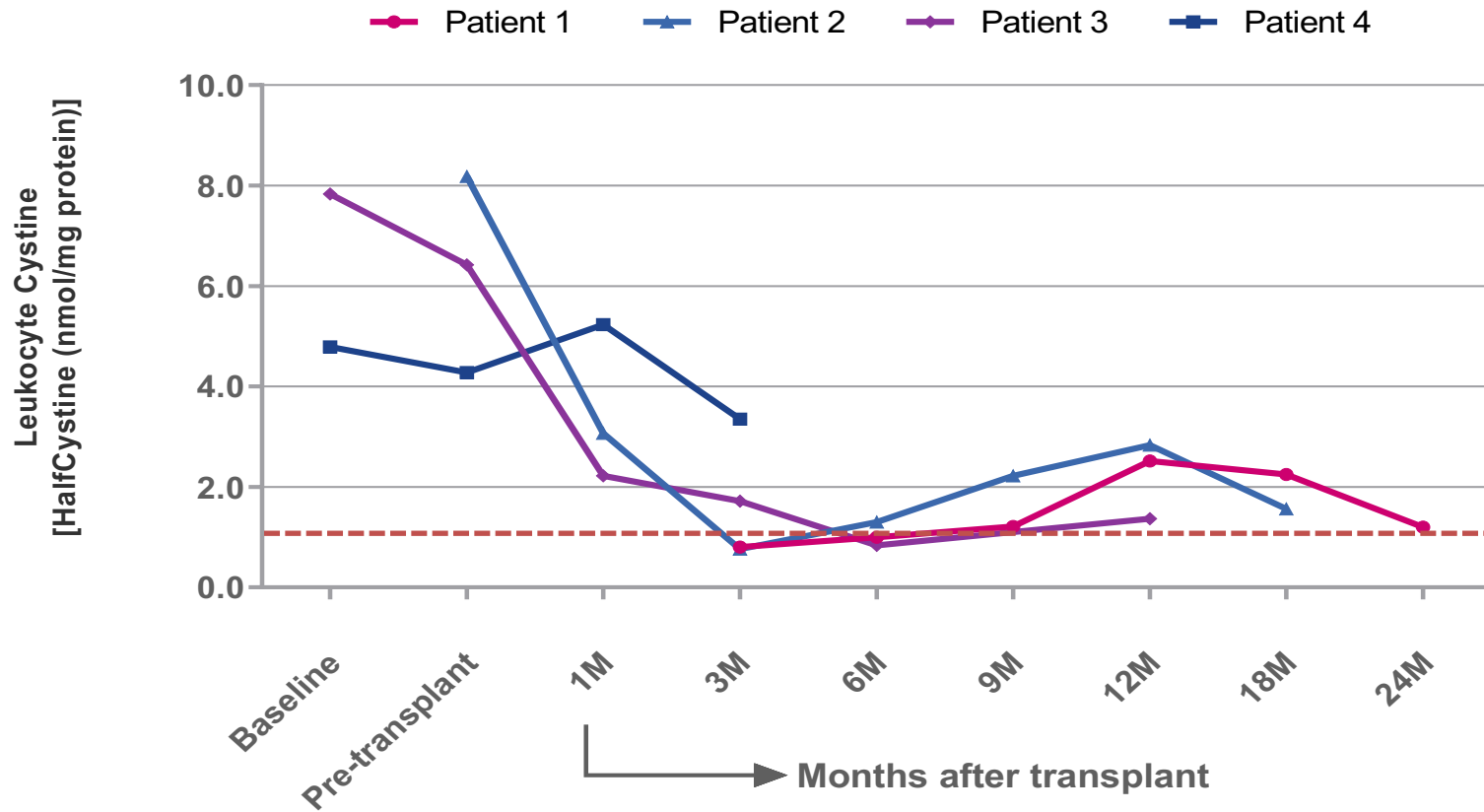
Drug Product (VCN/dg)	
Patient 1	2.1
Patient 2	1.3*
Patient 3	1.6
Patient 4	0.6



\* From second apheresis

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

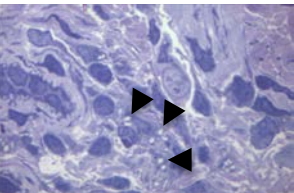
## LEUKOCYTE CYSTINE MEASURES



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

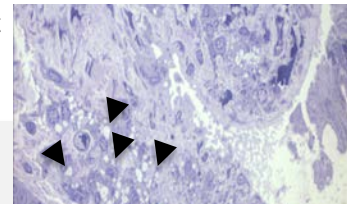


# TISSUE CYSTINE CRYSTALS: BIOPSIES



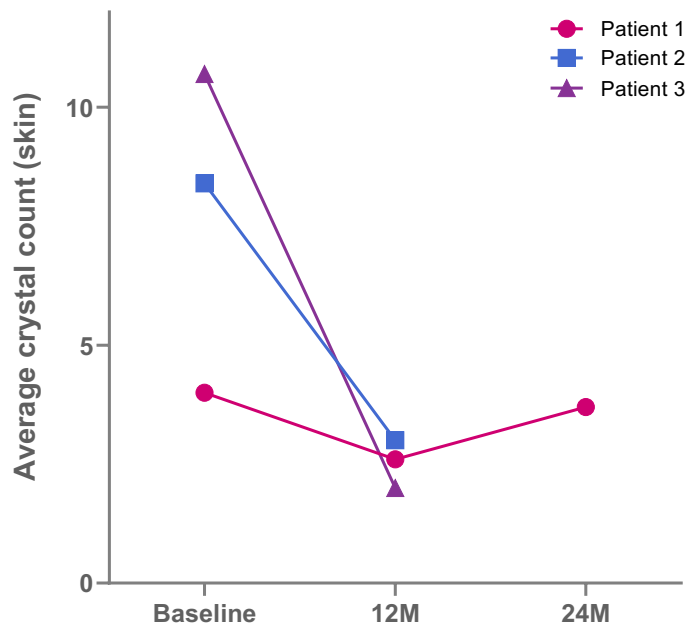
Skin biopsy image at Baseline - Patient 1

Rectal biopsy image at Baseline - Patient 1

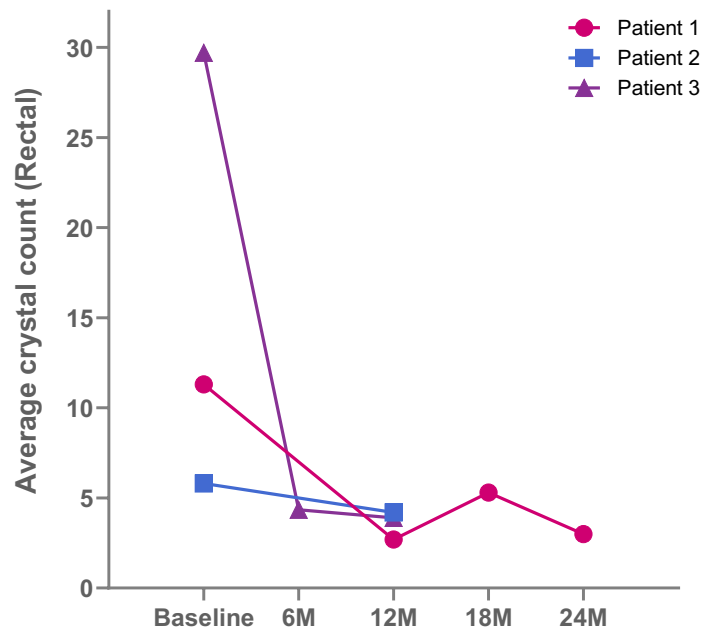


## Average intracytoplasmic crystals per cell

### Skin Biopsy

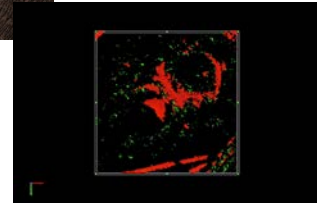


### Rectal Biopsy



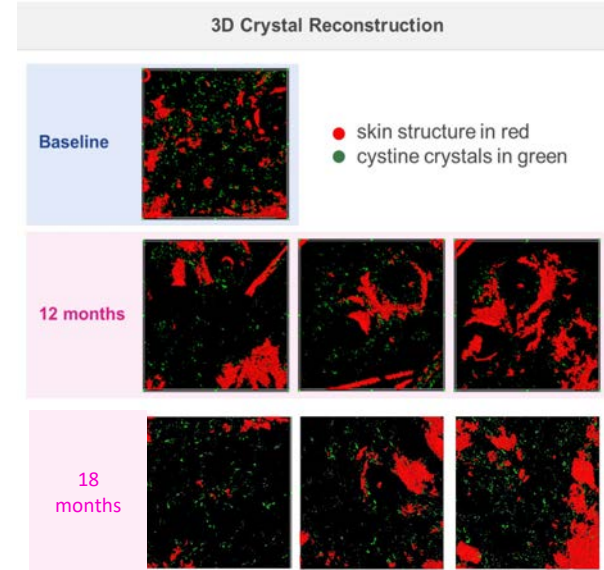
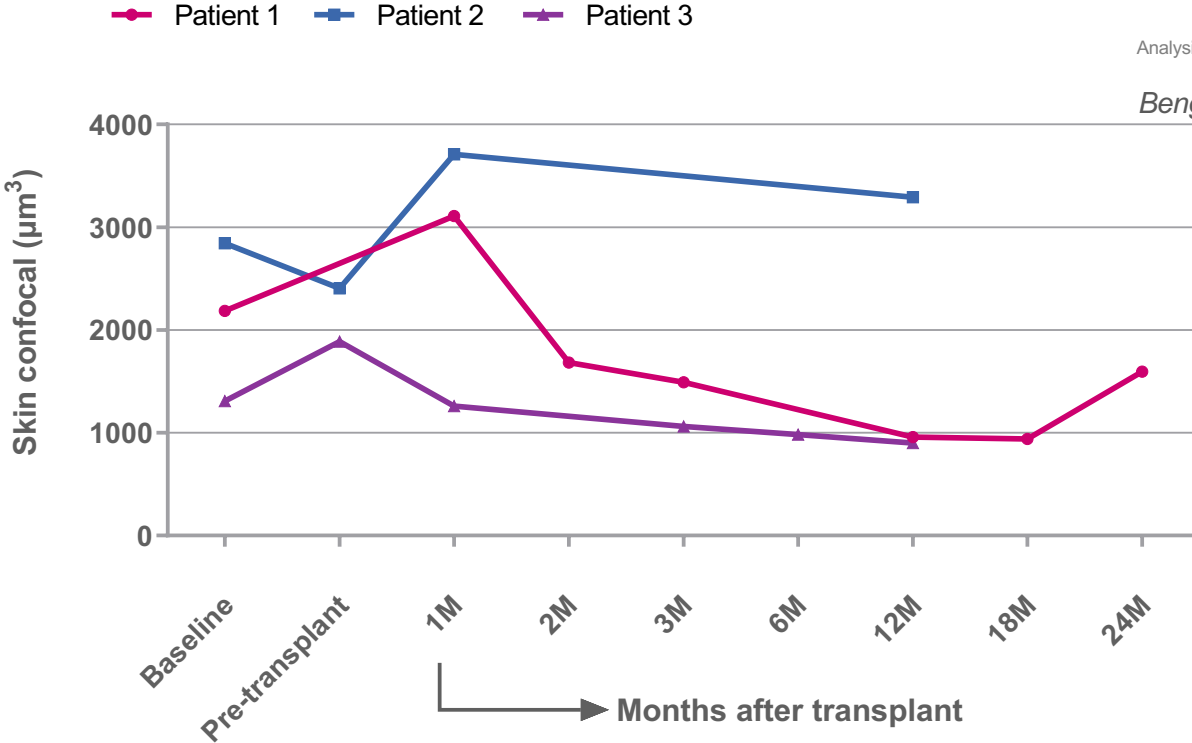
# TISSUE CYSTINE CRYSTALS IN THE SKIN: CONFOCAL

Exploratory endpoint



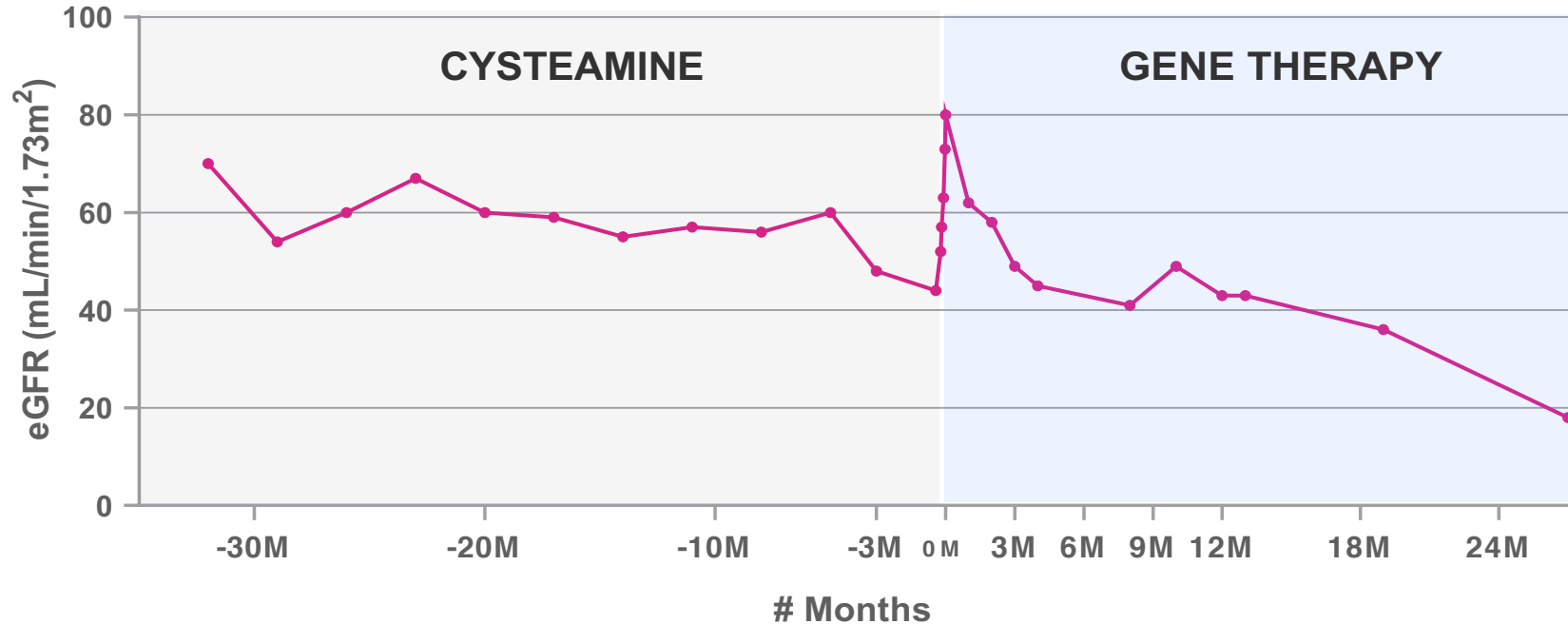
Analysis and quantification (3D Image-Pro software)

Bengali et al, PLOS ONE 2021



## PATIENT 1: KIDNEY FUNCTION

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



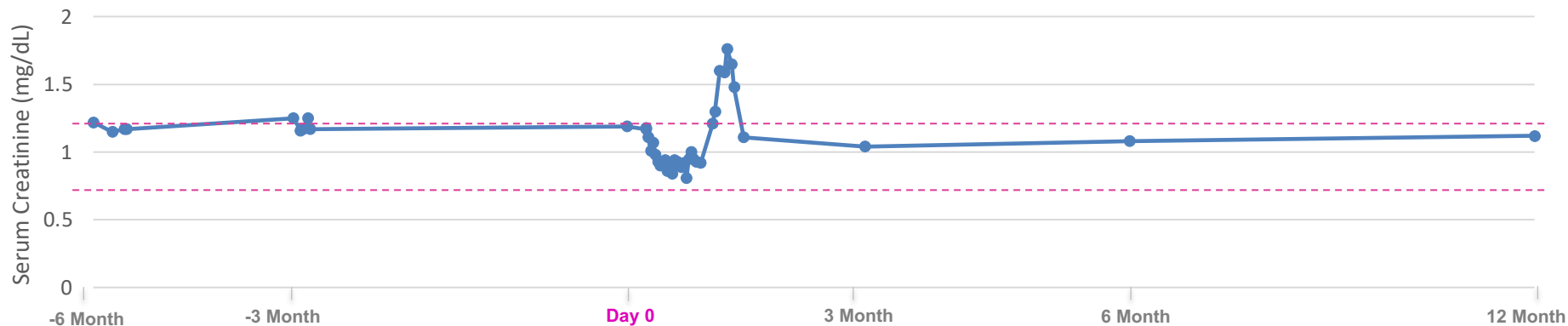
*\*Most of eGFR points represent an average of 2 to 8 eGFR value during the time period, except for Month 1 that represents an average of 29 eGFR values*

*PRELIMINARY DATA*

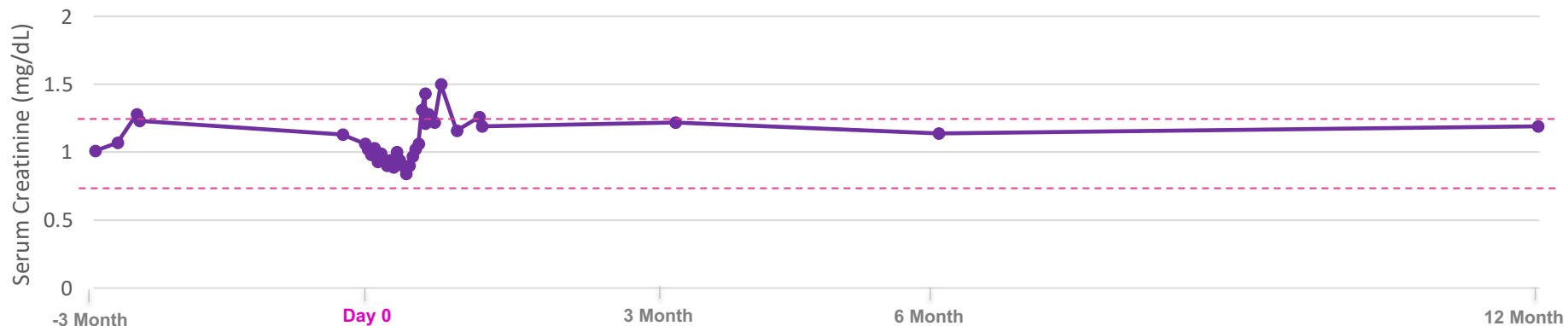
*eGFR: Estimated Glomerular Filtration Rate; eGFR calculated using CKD-EPI formula;*

## PATIENT 2 AND 3 – KIDNEY FUNCTION

Patient 2 - Serum Creatinine (mg/dL) Normal Range: 0.7 - 1.2

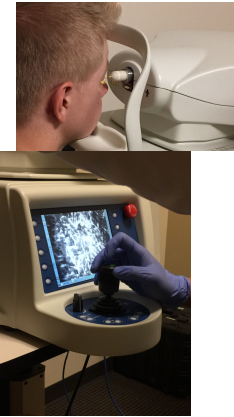


Patient 3 - Serum Creatinine (mg/dL) Normal Range: 0.7 - 1.2



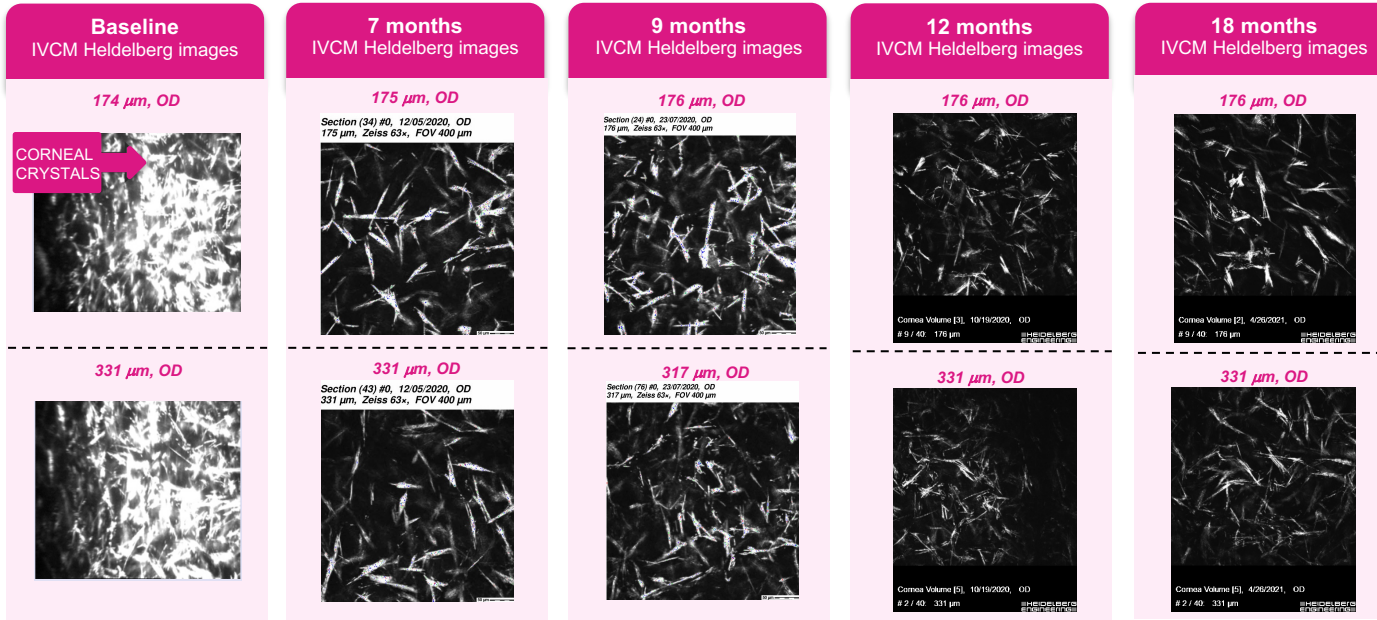
# PATIENT 1 – TISSUE CYSTINE CRYSTALS IN THE CORNEA

## Corneal confocal microscopy



Front of Cornea

Back of Cornea



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

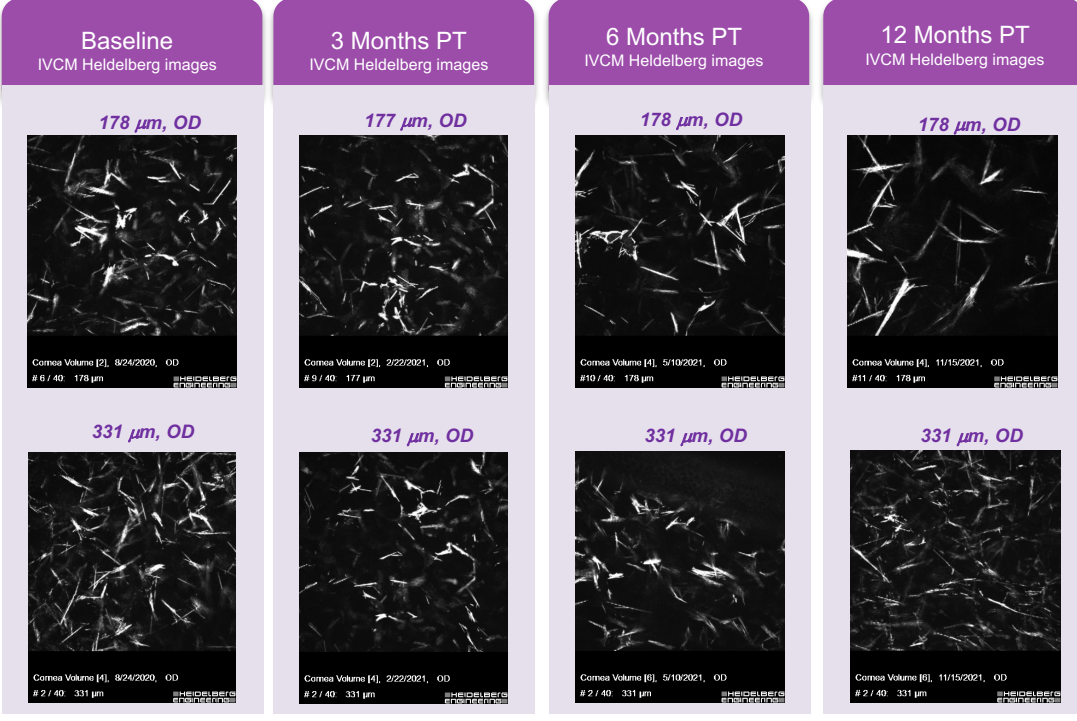
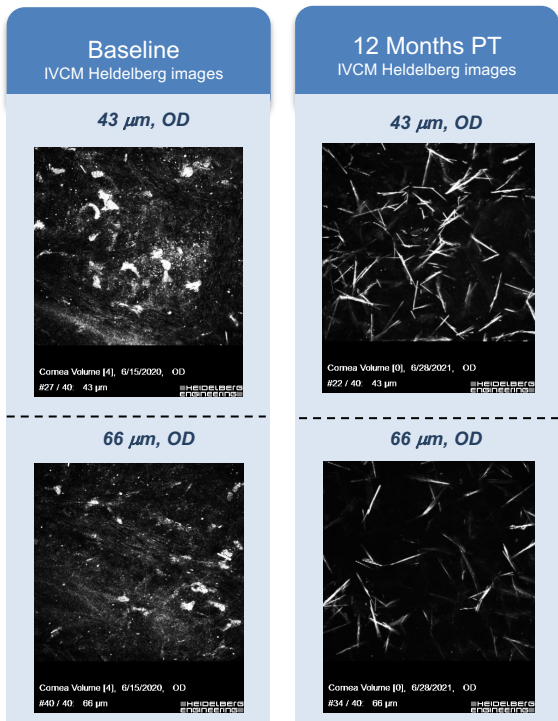
Scoring instructions: for each layer, assign a score of 0-4, where 0=no crystal; 1 <25%; 2=25-50%; 3=50-75%; 4>75%; Liang et al., IOVS 2015

## PATIENT 2 – TISSUE CYSTINE CRYSTALS IN THE CORNEA

## PATIENT 3 – TISSUE CYSTINE CRYSTALS IN THE CORNEA

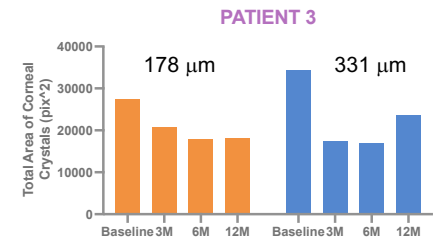
Front of Cornea

Back of Cornea



Photophobia Grade	
<b>Baseline</b>	2 or 3
<b>12 Months PT</b>	2

Photophobia Grade	
<b>Baseline</b>	2
<b>3 Months PT</b>	2.5
<b>6 Months PT</b>	3
<b>12 Months PT</b>	2

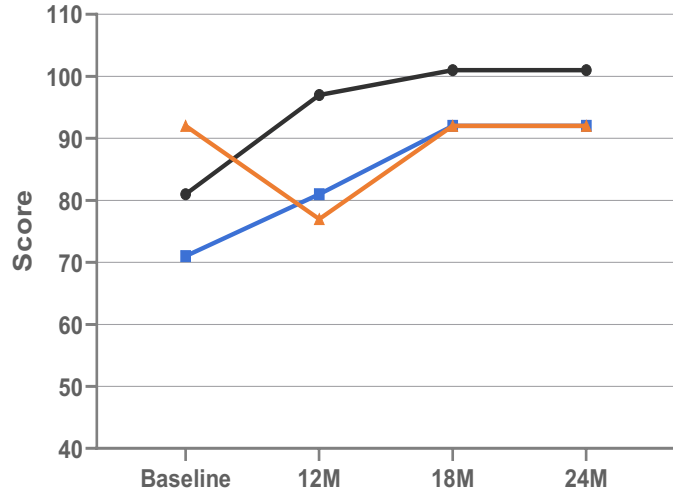


Score range: 1-5 where 1 is no photophobia and 5 is severe

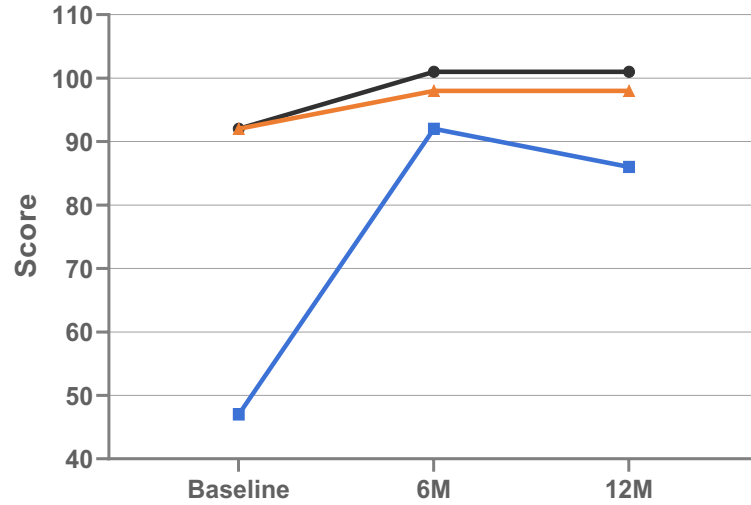
# NEUROCOGNITIVE ASSESSEMENTS

Dr. Doris Trauner

PATIENT 1



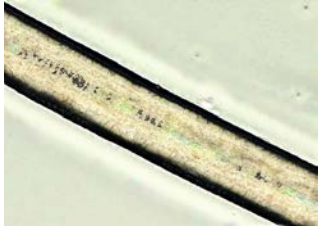
PATIENT 3



- 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



Baseline



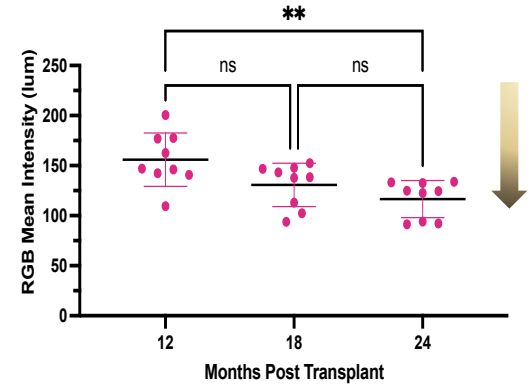
6 Months PT



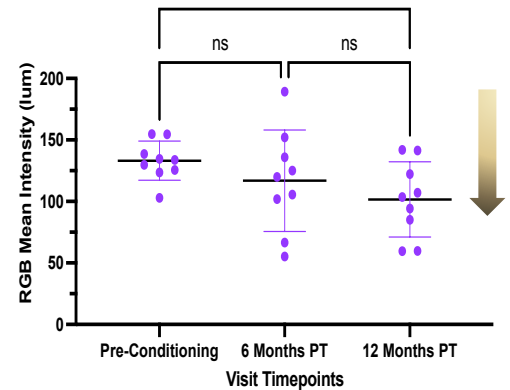
12 Months PT



CT.001 Hair color – RGB intensity










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



# ACKNOWLEDGEMENTS



Department of Pediatrics

Division of Genetics

Jay Sharma  
Maulik Panchal  
Anne Sawyers  
Imama Ahmed  
Priyanka Mishra  
Rafael Badell Grau  
Veenita Khare  
Anusha Sivakumar  
Thi Le  
Alexander Silva

Former members

Celine Rocca  
Laura Hernandez  
Spencer Goodman  
Tatiana Lobry  
Marya Bengali  
Peter Hevezi, Ph.D  
Swati Naphade, PhD  
Carlos Castellanos  
Betty Cabrera  
Frank Harrison  
Joseph Rainaldi  
Athena Lau  
Peter Hevezi, Ph.D  
Brian A. Yeagy, PhD  
Robert Cano  
Joseph Haquang  
Meisha Khan



UNIVERSITY of CALIFORNIA, SAN DIEGO  
SCHOOL OF MEDICINE



## The Cystinosis Stem Cell and Gene Therapy Consortium members

Bruce Barshop, MD – Theodore Ball, MD – Natalie Afshari, MD –  
Magdelene Dohil, MD – Ranjan Dohil – Nadine Benador, MD – Robert  
Mak, MD – Doris Trauner, MD

UC San Diego Health

CIRM Alpha Stem Cell Clinic

UC San Diego Health

Sanford Stem Cell Clinical Center

UC San Diego Health



Medical Personnel  
Patients



UCLA

Donald B. Kohn, MD

Julian Migley, MD

Alberta Children's Hospital

## FUNDING

