E-Poster

Results from First-In-Human Clinical Trial of RP-A501 (AAV9:LAMP2B) Gene Therapy Treatment for Danon Disease

Barry Greenberg[1], Emily Eshraghian[1], Pavan Battiprolu[2], Shilpi Epstein[2], Kimberly Hong[1], David Ricks[2], Tony Urey[1], Paul Yarabe[2], Andrew Kahn[1], Jonathan Schwartz[2], Kinnari Patel[2], Gaurav Shah[2] and José Trevejo[2]

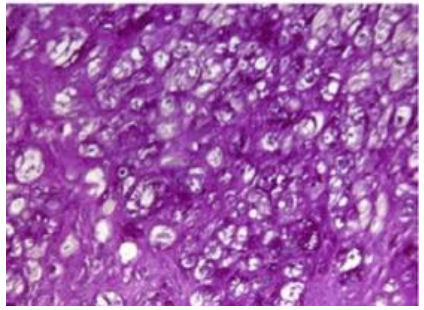
[1] University of California, San Diego Medical Center, La Jolla, CA

[2] Rocket Pharmaceuticals, Cranbury, NJ

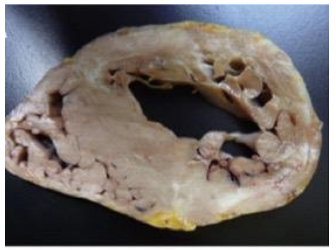
rocket pharma

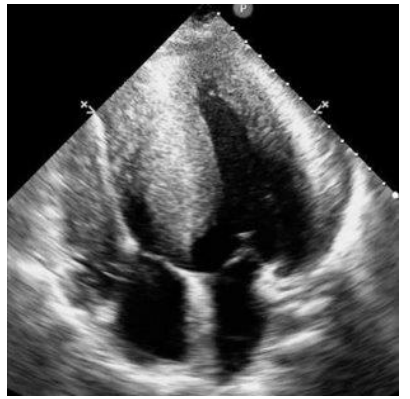
SEEKING CURES THROUGH GENE THERAPY

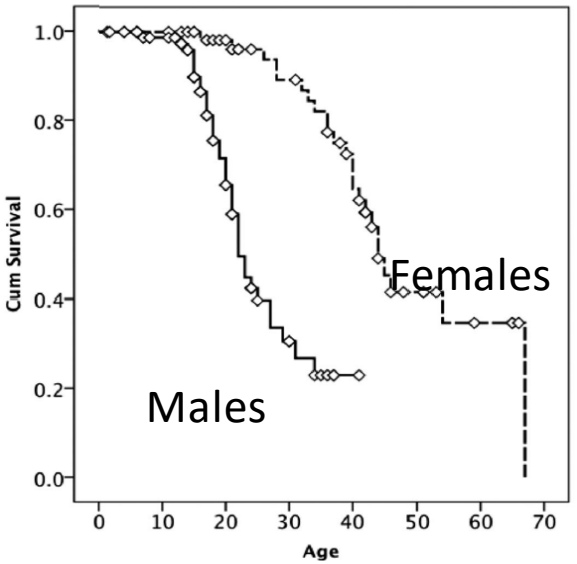
Danon Disease and the Potential for Gene Therapy



- Autosomal dominant, monogenic X-linked disease
  - *LAMP-2B* gene mutation
  - Impaired autophagy
- Severe Cardiomyopathy (CM 95%)
  - Males:
    - Hypertrophic CM with arrhythmias
    - Mortality in 2nd to 3rd decades
  - Females:
    - Dilated/hypertrophic CM and arrhythmia
    - Mortality in 4th to 5th decades
- Other Clinical Manifestations
  - Skeletal Myopathy
  - CNS manifestations
  - Ophthalmologic manifestations
- Heart transplant is current standard of care
- Gene Therapy (GT) introduces recombinant human genetic material in order to alter levels of a protein that will directly or indirectly (e.g. paracrine or systemic effects) alter organ structure and function.

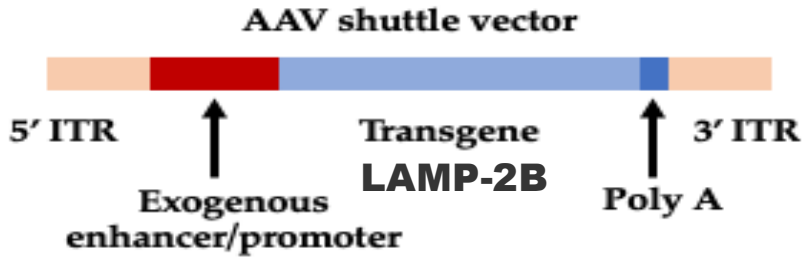






Boucek D, Jirikowic J, Taylor M. Genet Med 2011; 13(6):563-68

Recombinant AAV-derived vectors



Modified from: Romano. Mater Methods 2019;9:2796.

UC San Diego Health System

RP-A501 Clinical Trial and Outcome Measures

Non-Randomized Open Label Phase 1 Study

- Male Danon Disease Patients
  - Adults (and Adolescent): ≥15 year
  - Pediatrics: 8-14 years
- Single Intravenous Dose of RP-A501
  - Low Dose: 6.7 x 1013 GC/kg*
  - High Dose**: 1.1 x 1014 GC/kg*
- Select Inclusion Criteria
  - Male
  - Confirmed *LAMP2B* mutation
  - Cardiac involvement confirmed by echocardiogram, MRI or ECG
  - NYHA Class II or III symptoms
- Select Exclusion Criteria
  - LVEF <40% at baseline
  - Anti-AAV9 neutralizing antibody titer > 1:40
  - History of stroke or TIA

Intravenous Administration of RP-A501

- rAAV9 DNA expresses LAMP2B gene
- AAV9 demonstrates tropism to cardiomyocytes, skeletal muscle, liver and brain tissue
- Non-dividing, terminally differentiated cardiomyocytes can be transduced

Primary Outcomes

- Safety at each dose level
- Target tissue transduction & LAMP2B expression
- Effect on cardiomyocyte histology
- Clinical stabilization or improvement

UC San Diego Health System

*Genome copies/kilogram

** No further enrollment at this dose

RP-A501: Baseline Patient Status

COHORT	PATIENT ID	AGE	WEIGHT (kg)	NYHA CLASS	SIX MINUTE WALK (meters)	LVPWd* (mm)	IVSd* (mm)	LV EF* (%)	PCWp (mmHg)	BNP (pg/mL) [<100 pg/mL]	CPK (U/L) [<175 U/L]	LIVER FUNCTION	
												AST (U/L) [<40 U/L]	ALT (U/L) [<40 U/L]
Adult - Low Dose	1001	17 years	52.2	II	443	16.4	12	62	11	70	911	197	120
	1002	20 years	89.1	II	405	22.4	28.3	59	19	1104	175	95	51
	1005	18 years	91.8	II	427	17	14	59	13	161	2598	358	359
Adult – High Dose	1006	21 years	82.7	II	436	15	14	47	14	123	920	184	161
	1007	20 years	96.7	II	434	22.7	17.9	35	26	630	351	108	88

* All echocardiographic parameters from local lab reads; central lab assessment pending

UC San Diego Health System

RP-A501: Dose-Related Immune Response to rAAV Gene Therapy

Low Dose Adult
Age ≥15 years
$6.7x10^{13}$ GC*/kg

Enrolled n=3

Observed Adverse Effects:

Immediate
- Fever (1/3)
- Fatigue (1/3)
- Constipation (2/3)
- Nausea/vomiting (3/3)

Early
- Complement Activation (2/3)*
- Thrombocytopenia (2/3)
- Early Transaminase Elevation (3/3)
- D-dimer Elevation (3/3)

Delayed
- Delayed Transaminase Elevation (2/3)
- Steroid Induced-Myopathy (2/3)

High Dose Adult
Age ≥15 years
$1.1x10^{14}$ GC*/kg

Enrolled n=2***

Observed Adverse Effects:

Immediate
- Fever (1/2)
- Fatigue (2/2)
- Constipation (1/2)
- Nausea/vomiting (1/2)

Early
- Complement Activation (1/2)**
- Thrombocytopenia (2/2)
- Early Transaminase Elevation (2/2)
- D-dimer Elevation (1/2)
- TMA with Acute Renal Failure (1/2)**

Delayed
- Delayed Transaminase Elevation (1/2)
- Steroid Induced-Myopathy (2/2)

Modified Study Protocol to Mitigate Risk:
- No further enrollment at HIGHER dose
- Adjusted immunosuppressive regimen
  - Corticosteroids: Limit daily dose
  - Sirolimus: Minimize renal impact
  - Frequent monitoring for early signs of TMA
  - Continue rituximab

*All observed adverse effects in the Low and High Dose Adult and Adolescent cohorts were **reversible**.*

UC San Diego Health System

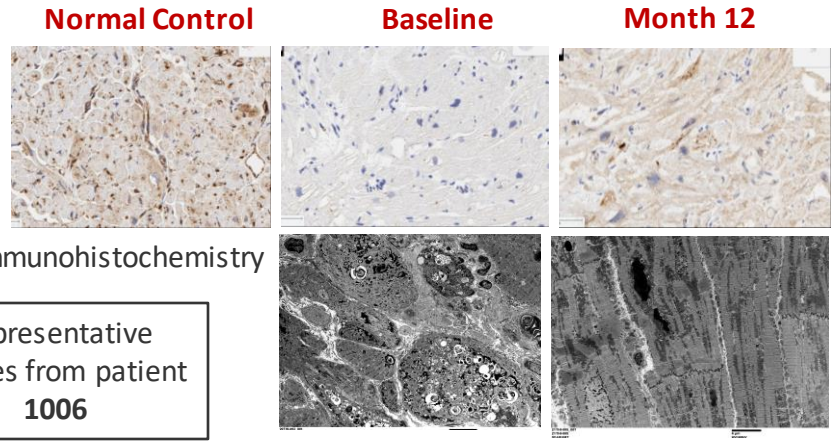
* Not monitored for in initial patient

*** No further enrollment at this dose

** Patient that developed thrombotic microangiopathy (TMA) with acute renal failure requiring transient hemodialysis with complete renal function recovery.

RP-A501: Low and High Dose Adolescent and Adult Cohorts

- First in-human gene therapy for monogenic cardiomyopathy
- RP-A501 r-AAV generally well tolerated at 6.7x10^{13} GC/kg dose level
  - Tailored immunosuppressive regimen
  - Transient and reversible immunologic response with no lasting clinical sequelae
- Histologic evidence of LAMP2B gene expression that is sustained at both doses tested
  - Cellular level (endomyocardial biopsies)
    - Improved LAMP2B protein expression
    - Decreased vacuoles and improved architecture on electron microscopy



Cohort	Patient ID	Variable	Baseline	Most Recent Follow-up	Time of Follow-up
Adult - Low Dose	1001	BNP (pg/mL)	70	30	24 months
		LVPWd* (mm)	16.4	17.9	
		NYHA class	II	II	
		6 MWT (meters)	443	467	
	1002	BNP (pg/mL)	942	200	18 months
		LVPWd* (mm)	22.4	12.1	
		NYHA class	II	I	
		6 MWT (meters)	405	410	
	1005	BNP (pg/mL)	176	44	15 months
		LVPWd* mm)	17	15.4	
		NYHA class	II	I	
		6 MWT (meters)	427	435	
Adult - High Dose	1006	BNP (pg/mL)	123	41	12 months
		LVPWd* (mm)	15	13	
		NYHA class	II	I	
		6 MWT (meters)	436	492	
	1007	BNP (pg/mL)	630	**	**
		LVPWd* (mm)	22.7	**	
		NYHA class	II	**	
		6 MWT (meters)	434	**	

Clinical parameters improved or remained stable

- NYHA class improved or stabilized
- 6-minute walk distance remained stable
- BNP decreased or stabilized
- LV wall thickness decreased or stabilized with improved or stable ejection fraction by 12 months
- Cardiac output improved or stabilized at cardiac catheterization

* All echocardiographic parameters from local lab reads; central lab reads pending

** Patient underwent heart transplant within 6 months due to continued progression of end-stage Danon disease

UC San Diego Health System

Acknowledgements

UC San Diego Health System

Jennifer Attias
Emily Eshraghian, MPH
Eric Adler, MD
Quan Bui, MD
Chamindra Konersman, MD
Ana Maria Manso, PhD

University of Colorado Anschutz Medical Campus
Children's Hospital Colorado

Matthew Taylor, MD, PhD

Children's Hospital of Philadelphia®

Joseph Rossano, MD, MS, FAAP, FACC
Abigail Waldron
Danielle Burstein, MD
Lindsey George, MD
Andrew Glatz, MD
Kimberly Lin, MD
Matthew O'Connor, MD
Carol Wittlieb-Weber, MD

rocket pharma

José Trevejo, MD PhD
Shilpi Epstein, MD
Pavan Battiprolu, PA, PhD
Sydney Reilly
David Ricks, PhD
Jonathan Schwartz, MD
Paul Yarabe, MBA

For more information:
Danonclinicaltrial@rocketpharma.com