Safety Profile of the First Pediatric Cardiomyopathy Gene Therapy Trial: RP-A501 (AAV9:LAMP2B) for Danon Disease

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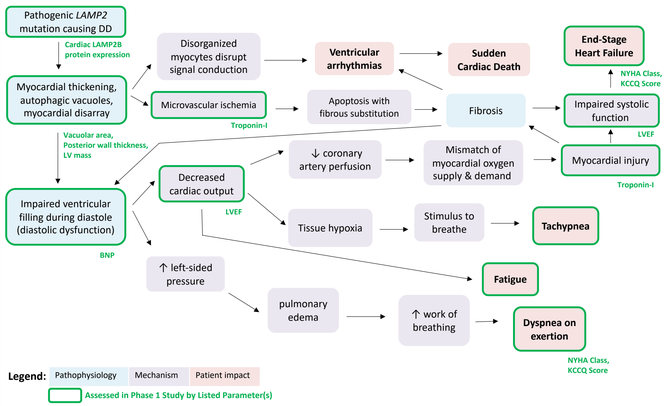
Poster #375

Introduction

Danon Disease

- Rare, X-linked dominant disorder caused by loss-of-function *LAMP2* mutations that impair autophagy
- Lysosome-Associated Membrane Protein 2 (LAMP2) consists of three splice isoforms (LAMP2-A, -B, & -C)
- LAMP-2B is the predominant isoform expressed in cardiomyocytes and is associated with macroautophagy (1)
- Cardinal histologic findings are numerous myocardial autophagic vacuoles and myocardial disarray
- Males develop **severe hypertrophic cardiomyopathy** with rapid progression to end-stage HF and death by their late teens
- Standard of care: ICD placement, anti-arrhythmic & CHF medications – none markedly modify disease progression
- DD represents a significant unmet need, as heart transplant is the only specific therapy. Transplant is not curative for the full spectrum of DD and 10-year survival post-transplant is 47% in pediatric HCM (2)
- Male DD patients also suffer from mild skeletal myopathy, cognitive impairment and retinopathy (3)
- Recent registry-based HCM studies suggest that *LAMP2* mutations underlie between 1-4% of HCM, suggesting a worldwide prevalence of 15,000-30,000 in US & Europe (3, 4)

Pathophysiology and Clinical Manifestations of Danon Disease HCM



Adapted from Jones & Arnold. (2014). Hypertrophic Cardiomyopathy: Pathogenesis and Clinical Findings

Study Design

Non-randomized open label study in male DD patients

Adults (& Adolescents): ≥15 years
- n=5, at UCSD

Pediatric: 8-14 years
- n=2, both at CHOP

Single Intravenous Dose of RP-A501 (AAV9.LAMP2B)

Low Dose: 6.7 x 10^{13} GC/kg

High Dose*: 1.1 x 10^{14} GC/kg (n=2)

* No further enrollment at this dose.

GC/kg: Genome copies / kilogram

Primary Outcomes

- **Acute and long-term safety**
- Target tissue transduction and *LAMP2B* expression
- Effect on myocardial morphology
- Clinical stabilization or improvement

Key Eligibility Criteria

Inclusion Criteria:

- DD diagnosis with confirmed pathologic *LAMP2B* mutation
- Male
- Cardiac involvement confirmed by imaging or ECG
- New York Heart Association (NYHA) Class II or III
- Able to walk >150 meters unassisted during 6-minute walk test (6MWT)

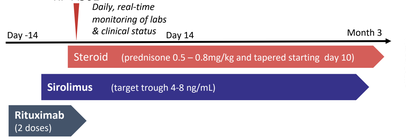
Exclusion Criteria:

- Anti-AAV9 neutralizing antibody titer >1:40
- Cardiopulmonary instability
- Prior organ transplantation
- LVEF <40% (implemented prior to enrolling pediatric cohort)

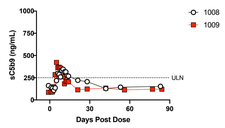
Additional details at ClinicalTrials.gov

Safety and Monitoring: Phase 1 Pediatric Patients

Pediatric Immunomodulation Protocol:



sC5b9 Evaluation Post RP-A501



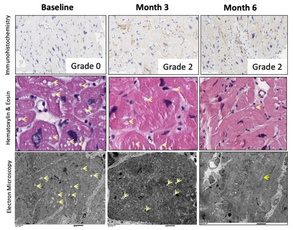
RP-A501 was well tolerated in pediatric cohort

- *No immediate, early or delayed RP-A501 related SAEs observed to date with enhanced immunomodulation*
  - **Minimal complement activation**
  - **Platelets remained within normal range**
  - **No complement-related clinical or laboratory AEs**
  - No reported **skeletal myopathy or late LFT elevation** with initial steroid dose-reduction and more rapid taper, and introduction of sirolimus
- *All AEs were transient and reversible*

Data cut-off August 19, 2022 with source data verification through July 11, 2022.

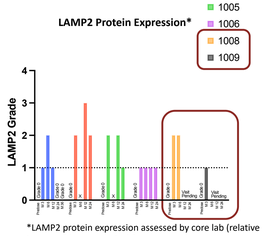
Impact of RP-A501 Gene Therapy on Molecular and Clinical Endpoints in Pediatric Patients

A501-008-1008 Endomyocardial Biopsy (EMB) Images



Similar findings on EMB from patient 1009 at Baseline and Month 3
H&E images captured at 20x magnification, presented digitally zoomed
Arrows indicate autophagic vacuoles

LAMP2 Protein Expression*



*LAMP2 protein expression assessed by core lab (relative to normal human controls):
Grade 0: negative staining; Grade 1: ≤ 25%; Grade 2: 26%-50%; Grade 3: 51%-75%; Grade 4: >75%.

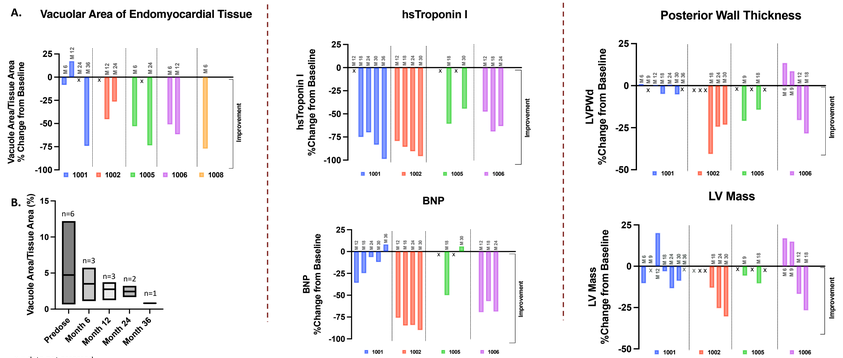
Patient ID	Baseline Status	Variable	Baseline[3]	Most Recent Follow-up	Time of Follow-up
A501-008-1008	Age at infusion: 12.3 years Max LV wall thickness: 41.9 mm z-score: +32 ICD: yes[1] WPW: yes 6MWT: 437 meters	% LAMP2 Protein[2]	0.5	21.1[4]	9 Months
		Troponin-I (ng/mL)	1.89	0.28	
		BNP (pg/mL)	1837	406	
		KCCQ-Overall Scale	50	92.7	
		NYHA Class	II	I	
A501-008-1009	Age at infusion: 11.7 years Max LV wall thickness: 19.8 mm z-score: +12 ICD: no WPW: no 6MWT: 553 meters	% LAMP2 Protein[2]	2.6	34.7[5]	6 Months
		Troponin-I (ng/mL)	0.67	0.07	
		BNP (pg/mL)	297	113	
		KCCQ-Overall Scale	52.1	81.3[6]	
		NYHA Class	II	I	

[1] Recommended prior to enrollment; ICD implanted 3 months after RP-A501
[2] All endomyocardial biopsies stained for LAMP2 were compared to normal control samples. Data is quantitated in a blinded fashion from ~3-5 sections
[3] Baseline values for troponin-I and BNP are the mean values from all pre-dose visits
[4] 6 month biopsy [5] 3 month biopsy [6] 3 month visit

Data cut-off September 27th, 2022 with source data verification through July 11, 2022.

Efficacy Update of All Phase 1 Patients

Cellular structure → Cardiac Structure and Function (Serology) → Cardiac Structure and Function (Echo)



x = data not assessed

Vacuolar area of endomyocardial tissue was quantified from H&E images. Data was quantified in a blinded manner using an AI tool. **A.** Data plotted for percentage vacuolar area of total tissue area from endomyocardial specimens pre- and post-gene therapy. **B.** Aggregate data indicating reduction across all cohorts. Bars denote minimum and maximum range, and line within each bar represents the mean value within study population.

Data cut-off August 19, 2022 with source data verification through July 11, 2022. Interim results are presented from the ongoing clinical study.

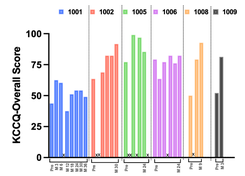
Functional Cardiac Status

NYHA Class at Enrollment and Most Recent Assessment

Cohort	Patient ID	Baseline	M12	Most Recent Follow-up	Time of Follow-up**
Low Dose Adult	1001*	II	II	II	36 months
	1002	II	III	I	30 months
	1005	II	II	I	30 months
High Dose Adult***	1006	II	I	I	24 months
Low Dose Pediatric	1008	II	October 2022	I	9 months
	1009	II	March 2023	I	6 months

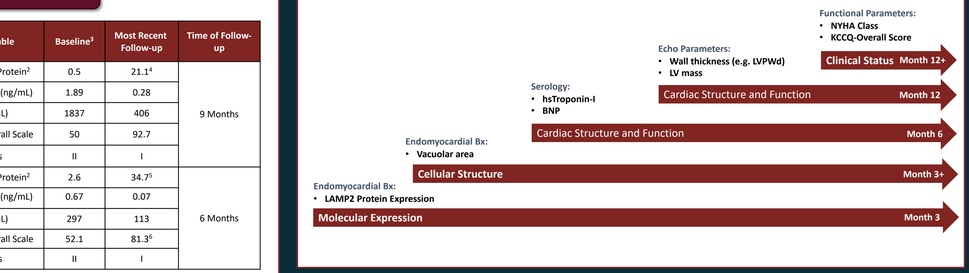
*Corticosteroid compliance uncertain **Last visit with verified data
***The 2nd Cohort 2 patient (1007) underwent heart transplant due to DD progression five months post RP-A501 infusion; as such, his data are not shown.

Kansas City Cardiomyopathy Questionnaire



x = data not assessed
Data cut-off September 27, 2022 with Source data verification through July 11, 2022.

Potential Efficacy Endpoints for Pivotal Study



Summary of Results and Conclusion

- **Pediatric Cohort:**
  - RP-A501 was well-tolerated in the pediatric cohort
  - T- and B-cell directed immunomodulation was associated with markedly reduced complement activation relative to adult cohorts
    - Minimal complement activation
    - Platelets remained within normal range
    - No complement-related clinical or laboratory AEs
  - Absent or limited worsening of skeletal myopathy with reduced steroid dose and more rapid taper, and introduction of sirolimus
  - No immediate, early or delayed RP-A501 related toxicities observed to date
  - Increased LAMP2B protein expression was associated with early signals of improved cardiac histology, and an improvement of serological markers indicative of myocardial injury and stress
- **Adult Cohort:**
  - Increased LAMP2B protein expression was associated with durable disease stabilization and improvement including clinical status (NYHA, KCCQ), LV hypertrophy (LV wall thickness and mass), biomarkers of myocardial injury and stress (hsTroponin I and BNP), and cardiac histology

In summary, RP-A501 was generally well-tolerated in adult and pediatric patients with Danon disease.

- Phase 1 enrollment and treatment are complete
- Enhanced immunomodulatory regimen appears well tolerated and effective in pediatric cohort
- Phase 1 efficacy in age ≥15 cohort: RP-A501 stabilizes and potentially improves Danon disease cardiomyopathy
- Early pediatric data are encouraging and consistent with adult efficacy
- These findings support phase 2 evaluation of RP-A501 in Danon disease

References

1. C. Chi *et al.*, (AMP-28 regulates human cardiomyocyte function by mediating autophagosome-lysosome fusion. *Proc Natl Acad Sci U S A.* (2018).
2. P. Thrush *et al.*, Pediatric heart transplantation – indications and outcomes in the current era. *J Thorac Dis.* 6, 1080-1096 (2014).
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Disclosures: **Rossano:** Consultant for the following: Abiomed, Bayer, Cytokinetics, Myokardia, and Novartis. **Lin:** There are no relationships to disclose. **Epstein:** Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. **Battiprolu:** Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. **Yarabe**: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. **Ricks:** Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. **Waldron:** There are no relationships to disclose. **Schwartz:** Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. **Greenberg:** Rocket Pharmaceuticals, Inc: Rocket Pharmaceuticals is the sponsor of a clinical trial for which Dr. Greenberg is the local site PI.