

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

**November 15, 2021**



SEEKING CURES THROUGH GENE THERAPY

# Important Information

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## Cautionary Statement Regarding Forward-Looking Statements

Statements made in this release may include statements which are not historical facts and are considered forward-looking within the meaning of the securities laws, and which are usually identified by the use of words such as “anticipates,” “believes,” “estimates,” “expects,” “intends,” “may,” “plans,” “projects,” “seeks,” “should,” “will,” and variations of such words or similar expressions. We intend these forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in Section 27A of the Securities Act and Section 21E of the Securities Exchange Act and are making this statement for purposes of complying with those safe harbor provisions. These forward-looking statements reflect our current views about our plans, intentions, expectations, strategies and prospects, which are based on the information currently available to us and on assumptions we have made. Although we believe that our plans, intentions, expectations, strategies and prospects as reflected in or suggested by those forward-looking statements are reasonable, we can give no assurance that the plans, intentions, expectations or strategies will be attained or achieved. Furthermore, actual results may differ materially from those described in the forward-looking statements and will be affected by a variety of risks and factors that are beyond our control including, without limitation, those set forth in our earnings release issued earlier today and in Item 1A. Risk Factors of our Annual Report on Form 10-K for the year ended December 31, 2020, as updated by our subsequently filed Quarterly Reports on Form 10-Q and our other SEC filings. We assume no obligation to update publicly any forward-looking statements, whether as a result of new information, future events or otherwise.

## Disclosures

Dr. Adler has stock options with Rocket Pharmaceuticals and is an inventor of intellectual property. UC San Diego is not endorsing or supporting Rocket Pharmaceuticals or its products.

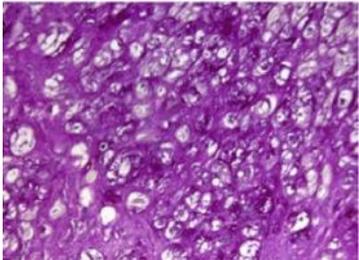


## Two Key Takeaways for Today

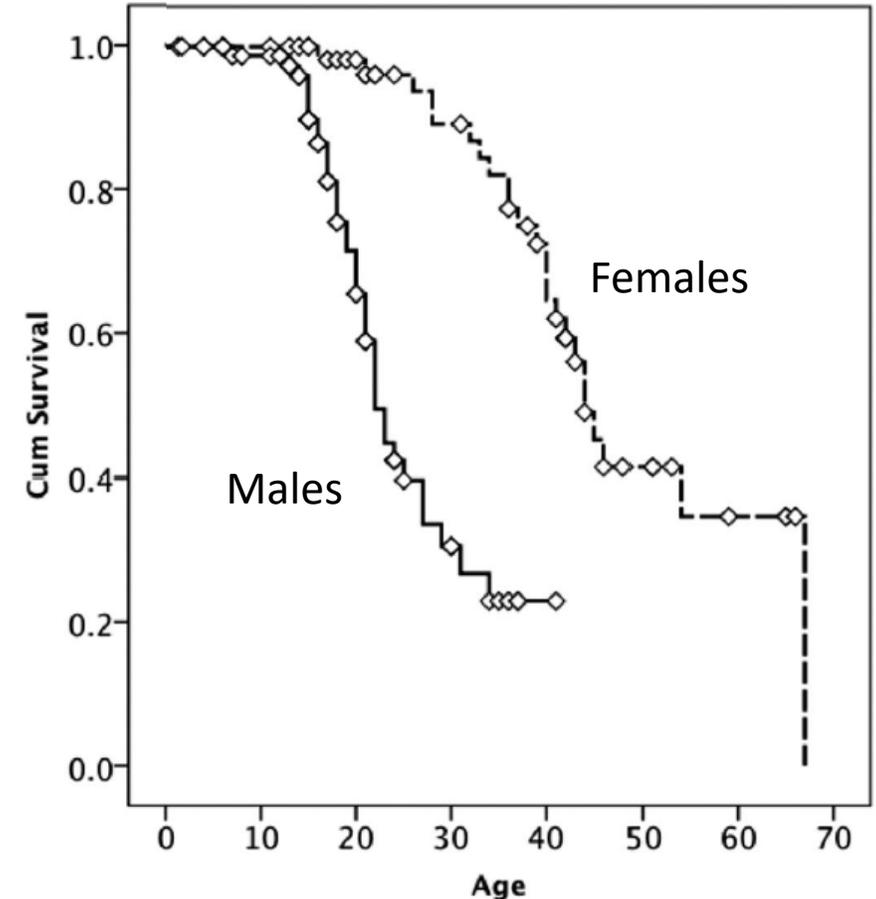
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1. In all patients who had closely monitored immunosuppression therapy in this trial we observed evidence of improvement in functional and clinical parameters
  - The one patient who was not closely monitored for immunosuppression therapy also demonstrated stabilization
2. Echocardiogram and invasive hemodynamic data supported the observed clinical improvements
  - In the closely monitored patients there is evidence that RP-A501 improved both the structure and function of the heart

# Danon Disease



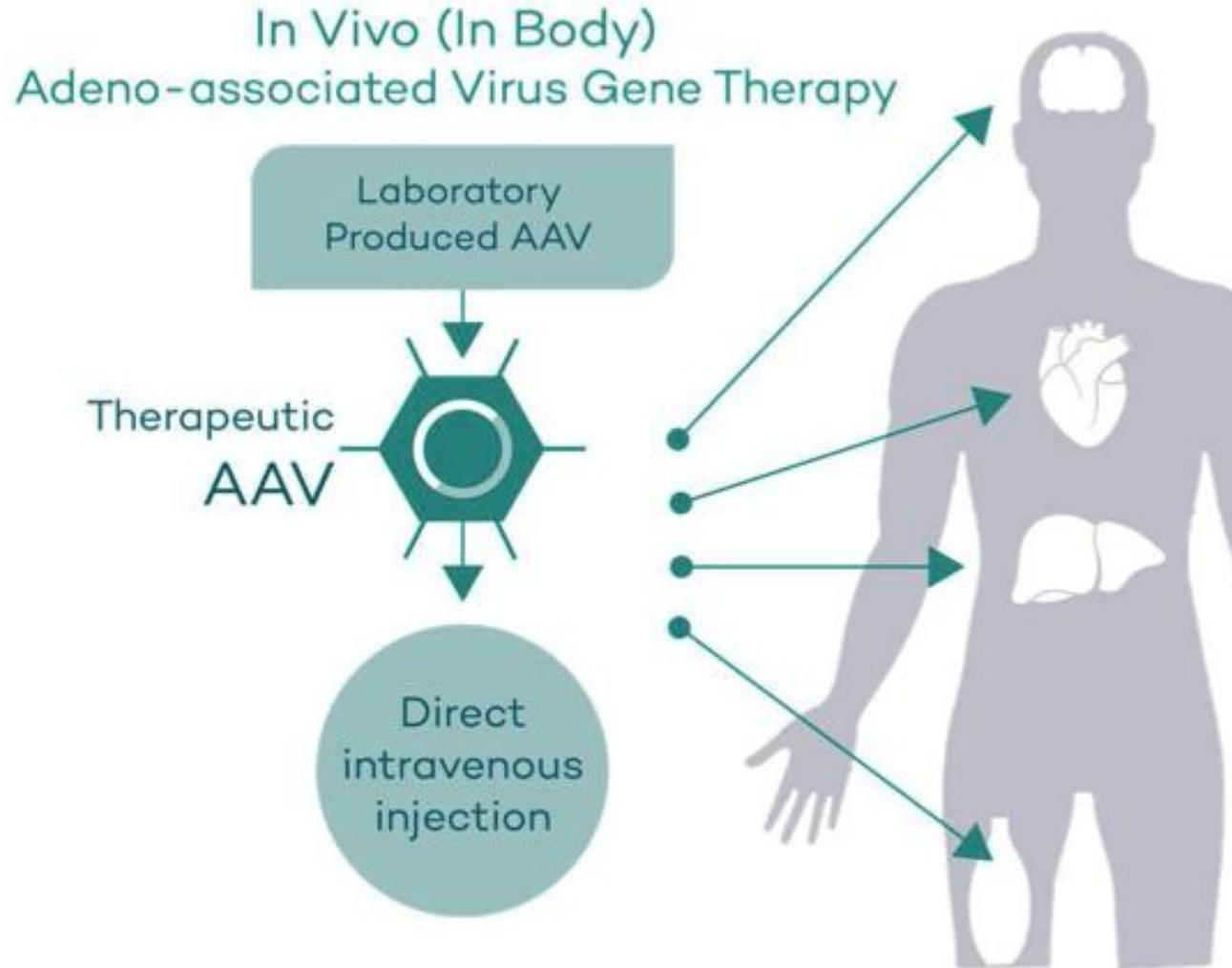
- **Autosomal dominant, monogenic X-linked disease**
  - *LAMP-2B* gene mutation
  - Impaired autophagy
- **Severe Cardiomyopathy (CM 95%)**
  - Mortality secondary to heart failure
  - **Males:**
    - Hypertrophic CM with arrhythmias
    - Mortality in 2nd to 3rd decades
  - **Females:**
    - Dilated/hypertrophic CM and arrhythmias
    - Mortality in 4th to 5th decades
- **Other Clinical Manifestations**
  - Skeletal Myopathy
  - CNS manifestations
  - Ophthalmologic manifestations
- **Heart transplant is current standard of care**



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



# How Does rAAV Gene Therapy (RP-A501) Work in Danon Disease?



## Intravenous Administration of rAAV

- AAV9 demonstrates tropism to:
  - Cardiomyocytes
  - Skeletal muscle
  - Liver
  - Brain tissue
- Non-dividing, terminally differentiated cardiomyocytes can be transduced
- rAAV9 DNA expresses LAMP2B gene

# RP-A501 Clinical Trial and Outcome Measures

Non-Randomized  
Open Label  
Phase 1 Study

## Study Design

- Male Danon Disease Patients
  - Adult and Adolescent:  $\geq 15$  years
  - Pediatrics: 8-14 years
- Single Intravenous Dose of RP-A501
  - Low Dose:  $6.7 \times 10^{13}$  GC/kg\*
  - High Dose:\*\*  $1.1 \times 10^{14}$  GC/kg\*

## Primary Outcomes

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

\*Genome copies/kilogram

\*\* No further enrollment at this dose



# RP-A501: Patient Entry Criteria

## Inclusion

- Male
- Confirmed *LAMP2B* mutation
- Cardiac involvement confirmed by echocardiogram, MRI or ECG
- NYHA Class II or III symptoms
- Ability to walk >150 meters unassisted during the 6-minute walk test (6MWT)
- **Adequate hematologic, hepatic and renal function\***
- Capacity to provide informed consent
- No contraindication for meningococcal vaccination (prior to RP-A501 administration)

## Exclusion

- Anti-AAV9 neutralizing antibody titer criteria
- **LVEF <40% at baseline**
- Acute or chronic respiratory failure on ventilatory support
- IV inotropes, vasodilators or diuretics within 30 days prior to enrollment
- Prior or current LVAD
- Prior organ transplantation
- Prior cardiac surgery or percutaneous cardiac intervention (for arteriothrombotic complications or valvuloplasty)
- **History of stroke or TIA**

\*Additional details @ClinicalTrials.gov, Bold indicates protocol updates



# RP-A501: Baseline Clinical Status and Biomarker Values

| Cohort            | Patient ID | Age at Enrollment | Weight (kg) | Clinical Status |                          | Biomarker           |
|-------------------|------------|-------------------|-------------|-----------------|--------------------------|---------------------|
|                   |            |                   |             | NYHA Class      | Six Minute Walk (meters) | BNP [ $<100$ pg/mL] |
| Adult - Low Dose  | 1001       | 17 years          | 52.2        | II              | 443                      | 70                  |
|                   | 1002       | 20 years          | 89.1        | II              | 405                      | 1104                |
|                   | 1005       | 18 years          | 91.8        | II              | 427                      | 161                 |
| Adult - High Dose | 1006       | 21 years          | 82.7        | II              | 436                      | 123                 |
|                   | 1007       | 20 years          | 96.7        | II              | 434                      | 630                 |

# RP-A501: Baseline Patient Status

## Hypertrophic Cardiomyopathy

1. Thickened myocardium
  - LV posterior wall
  - Interventricular septum
2. Preserved systolic function until late stage of disease
  - LV Ejection fraction
  - Cardiac output
3. Impaired diastolic function
  - Pulmonary capillary wedge pressure

| Cohort            | Patient ID | Age at Enrollment | Weight (kg) | Echocardiogram            |                  | Catheterization  |
|-------------------|------------|-------------------|-------------|---------------------------|------------------|------------------|
|                   |            |                   |             | Wall Thickness* [6-11 mm] | LV EF** [50-75%] | PCWp [8-12 mmHg] |
| Adult - Low Dose  | 1001       | 17 years          | 52.2        | 16.4                      | 62               | 11               |
|                   | 1002       | 20 years          | 89.1        | 22.4                      | 59               | 19               |
|                   | 1005       | 18 years          | 91.8        | 17                        | 59               | 13               |
| Adult - High Dose | 1006       | 21 years          | 82.7        | 15                        | 47               | 14               |
|                   | 1007       | 20 years          | 96.7        | 22.7                      | 35               | 26               |

\* Wall thickness refers to left ventricular posterior wall in diastole (LVPWd)

\*\* All echocardiographic parameters from local site assessment: LVEF=left ventricular ejection fraction

PCWp = pulmonary capillary wedge pressure



# RP-A501: High Dose Summary of Safety and Tolerability

**High Dose Adult and Adolescent**  
 Age ≥15 years  
 1.1x10<sup>14</sup> GC\*/kg

n=2\*  
 →

| <u>Immediate:</u> | <u>n</u> | <u>Early:</u>              | <u>n</u> | <u>Delayed:</u>          | <u>n</u> |
|-------------------|----------|----------------------------|----------|--------------------------|----------|
| Fever             | 1        | Complement activation      | 1**      | Transaminase elevation   | 1        |
| Fatigue           | 2        | Thrombocytopenia           | 2★       | Deep vein thrombosis     | 1        |
| Constipation      | 1        | Transaminase elevation     | 2        | Steroid-induced myopathy | 1        |
| Nausea/vomiting   | 1        | D-dimer elevation          | 1        | Ventricular arrhythmias  | 1        |
|                   |          | TMA w/ acute kidney injury | 1**      | Acute heart failure      | 1        |

**Currently-Implemented Protocol Risk Mitigation:**

- No further enrollment at HIGHER dose
- Adjusted immunosuppressive regimen
  - Corticosteroids: Limit daily dose
  - Sirolimus: Minimize renal impact
  - Frequent monitoring for early signs of TMA
  - Rituximab continued

\* No further enrollment at this dose

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

★ All Grade 1, except for Grade 4 in patient who developed TMA **Red colored font indicates Serious Adverse Event (SAE)**



# RP-A501: Low Dose Summary of Safety and Tolerability

**Low Dose Adult  
and Adolescent**  
Age ≥15 years  
6.7x10<sup>13</sup> GC\*/kg

n=3  
➔

| <u>Immediate:</u> | <u>n</u> | <u>Early:</u>          | <u>n</u> | <u>Delayed:</u>                 | <u>n</u> |
|-------------------|----------|------------------------|----------|---------------------------------|----------|
| Fever             | 1        | Complement activation  | 2*       | Transaminase elevation          | 2        |
| Fatigue           | 1        | Thrombocytopenia       | 2★       | <b>Steroid-induced myopathy</b> | <b>2</b> |
| Constipation      | 2        | Transaminase elevation | 3        | <b>Salmonella Sepsis</b>        | <b>1</b> |
| Nausea/vomiting   | 3        | D-dimer elevation      | 3        |                                 |          |

*RP-A501 was well tolerated and all adverse events in low & high dose adult/adolescent cohorts were reversible demonstrating a manageable safety profile*

\* Not monitored for in initial patient

★ All Grade 1

Red colored font indicates Serious Adverse Event (SAE)



# RP-A501: Stabilization or Improvement of Cardiac Biomarkers and Functional Status Across Dose Levels

| Cohort            | Patient ID | Variable       | Baseline | Most Recent Follow-up | Time of Follow-up |
|-------------------|------------|----------------|----------|-----------------------|-------------------|
| Adult - Low Dose  | 1001*      | NYHA class     | II       | II                    | 24 months         |
|                   |            | BNP (pg/mL)    | 70       | 30                    |                   |
|                   |            | 6 MWT (meters) | 443      | 467                   |                   |
|                   | 1002       | NYHA class     | II       | I                     | 18 months         |
|                   |            | BNP (pg/mL)    | 942      | 200                   |                   |
|                   |            | 6 MWT (meters) | 405      | 410                   |                   |
|                   | 1005       | NYHA class     | II       | I                     | 15 months         |
|                   |            | BNP (pg/mL)    | 176      | 44                    |                   |
|                   |            | 6 MWT (meters) | 427      | 435                   |                   |
| Adult - High Dose | 1006       | NYHA class     | II       | I                     | 12 months         |
|                   |            | BNP (pg/mL)    | 123      | 41                    |                   |
|                   |            | 6 MWT (meters) | 436      | 492                   |                   |

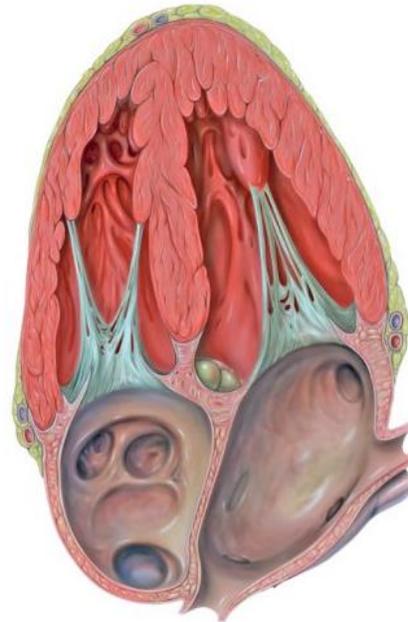
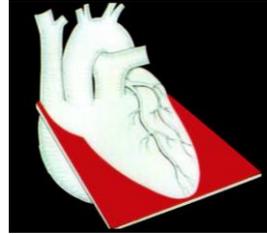
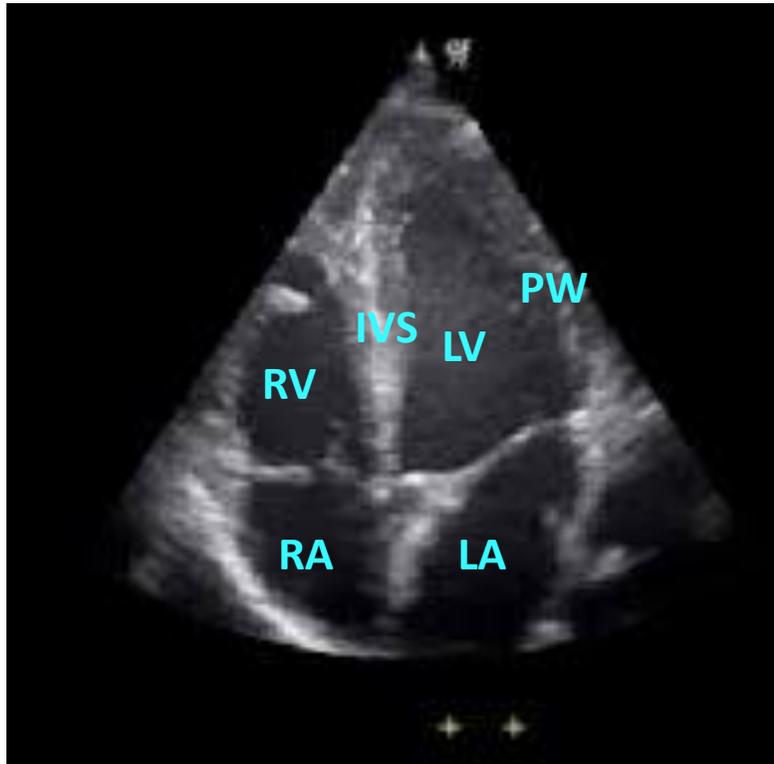
\* Corticosteroid compliance not monitored in initial patient  
 NYHA = New York Heart Association

BNP = Brain Natriuretic Peptide  
 6MWT = 6-Minute Walk Test

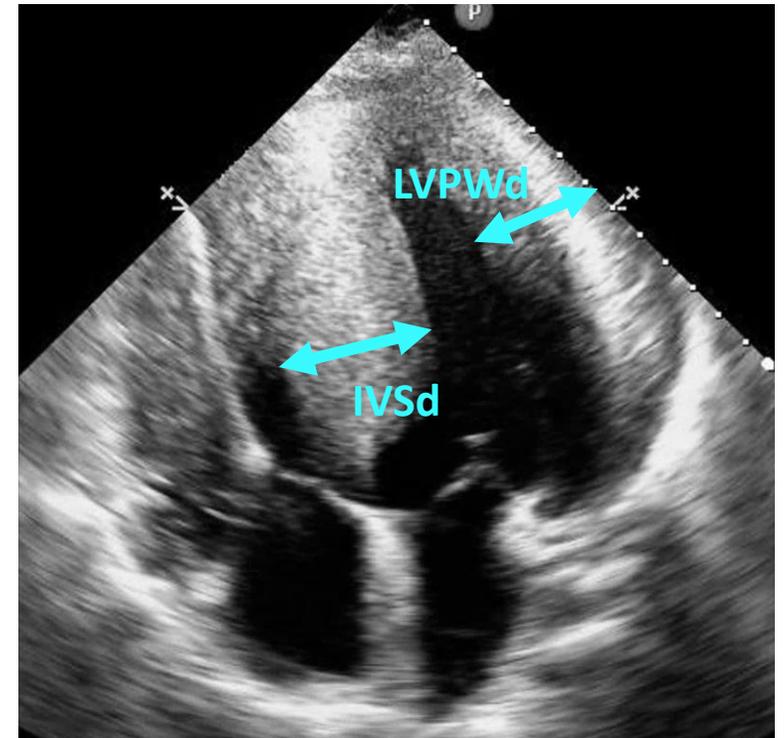


# RP-A501 Adolescent and Adult: Echocardiogram (Apical 4-Chamber View)

Normal



Danon Patient 1002

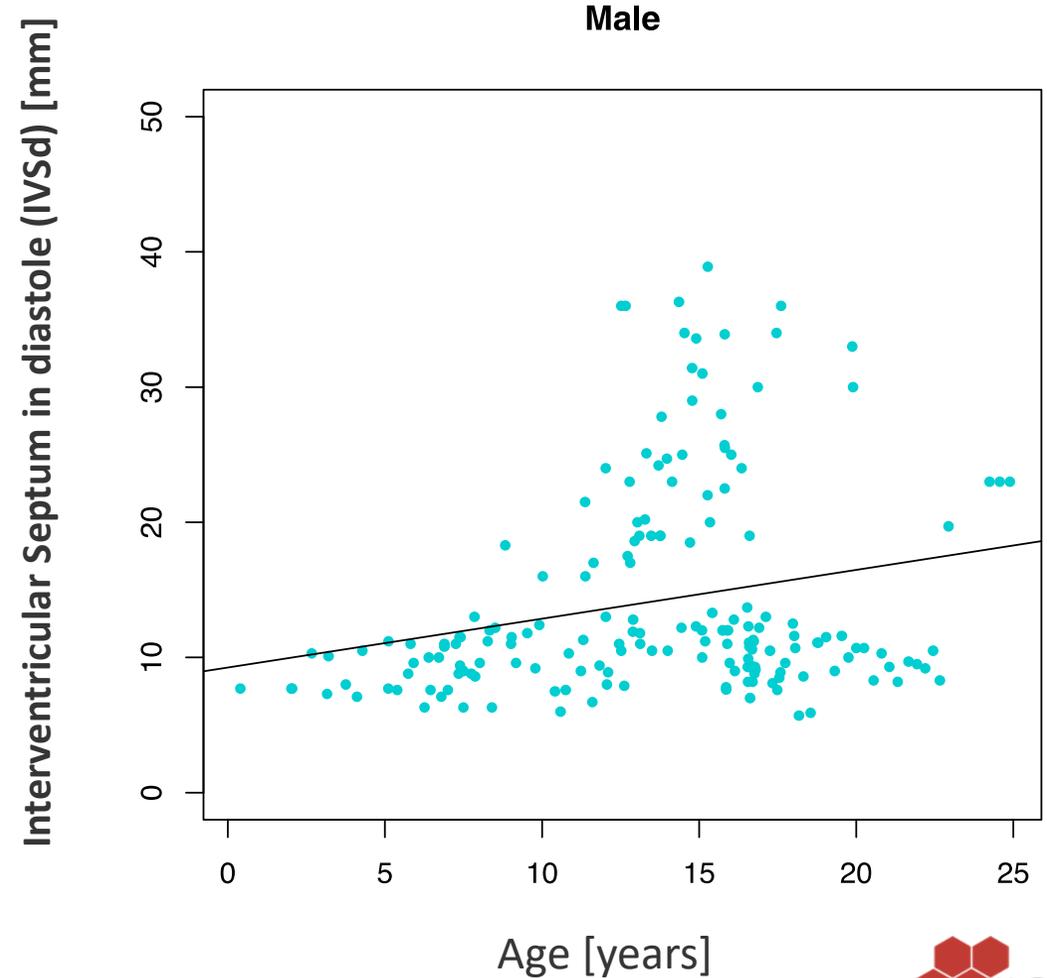
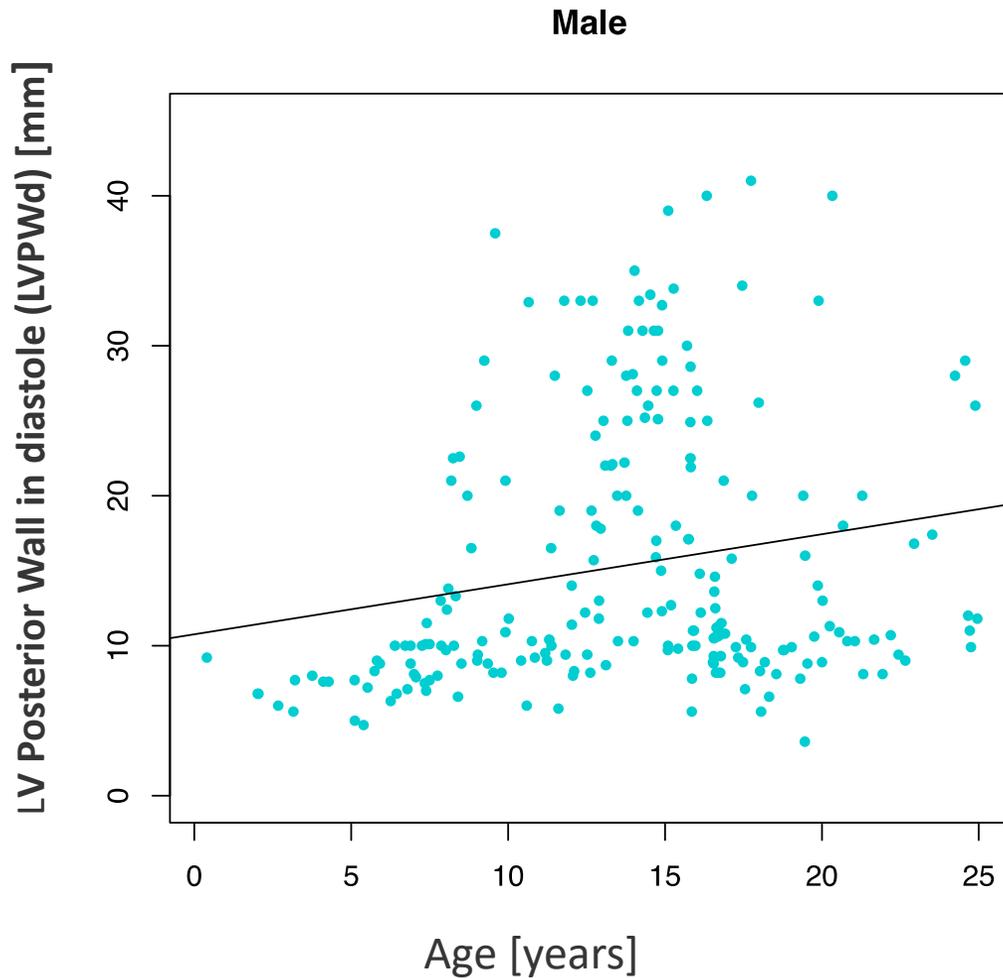


RA: right atrium  
RV: right ventricle  
IVS: interventricular septum  
LA: left atrium  
LV: left ventricle  
PW: posterior wall

LVPWd: LVPW in diastole  
IVSd: IVS in diastole



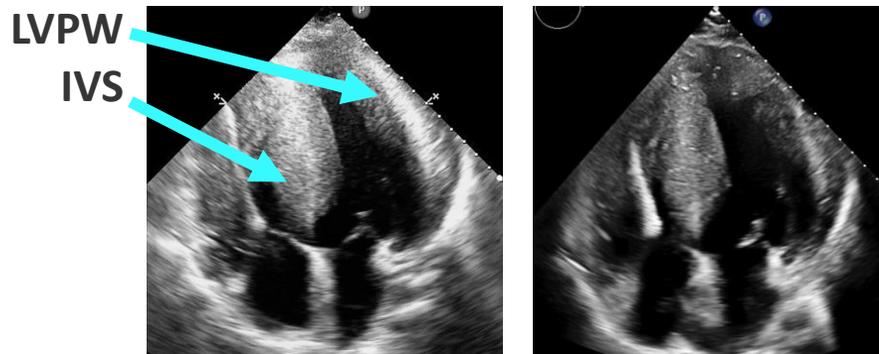
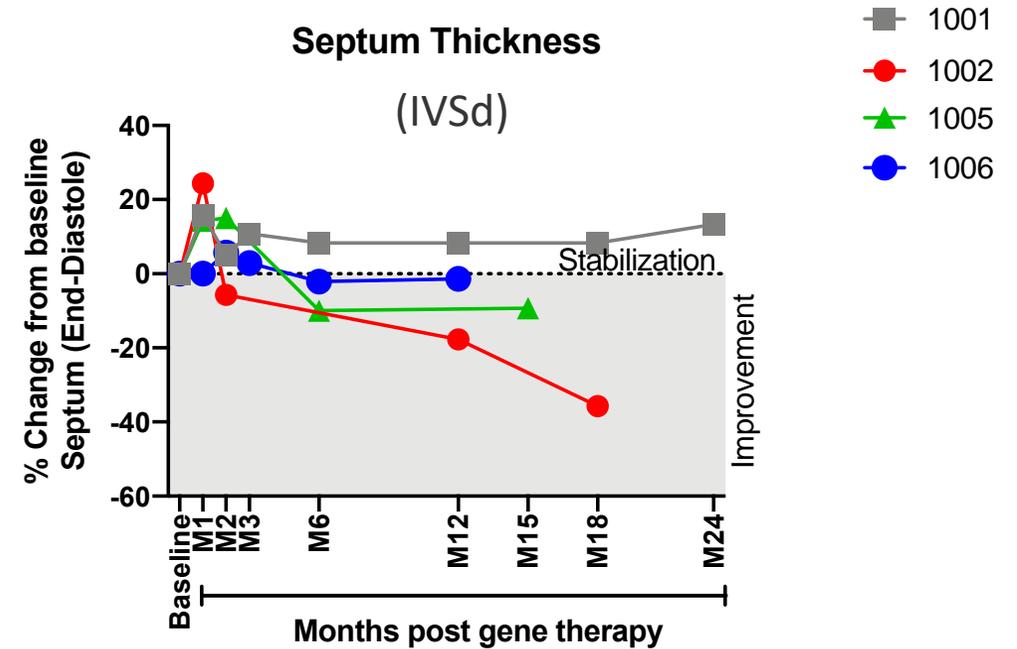
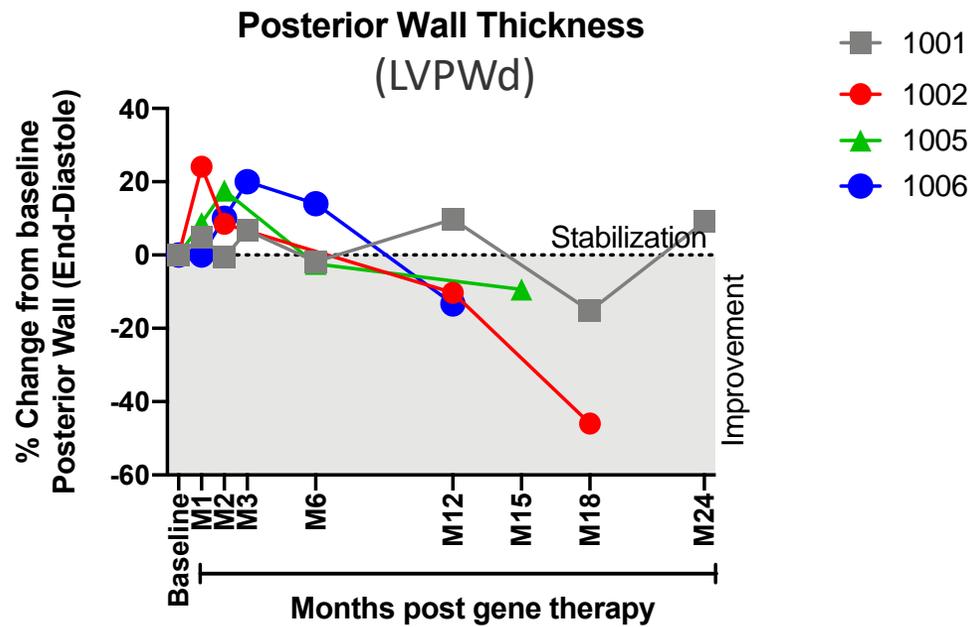
# Danon Natural History: LV Posterior & Septal Wall Thickness (Echo)



Retrospective Review of Echocardiograph Data from N=32 Male Danon Patients



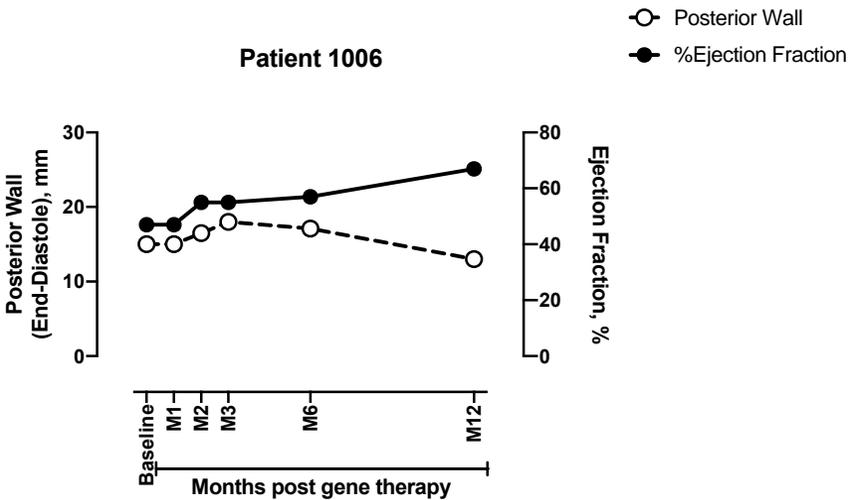
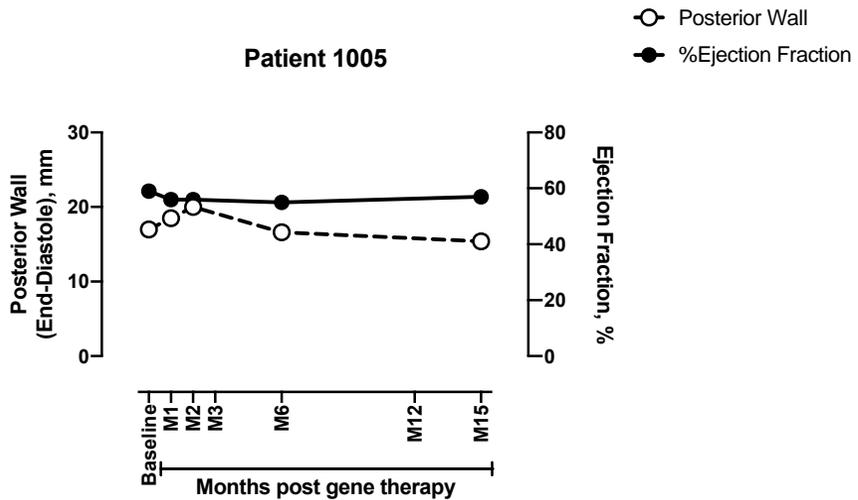
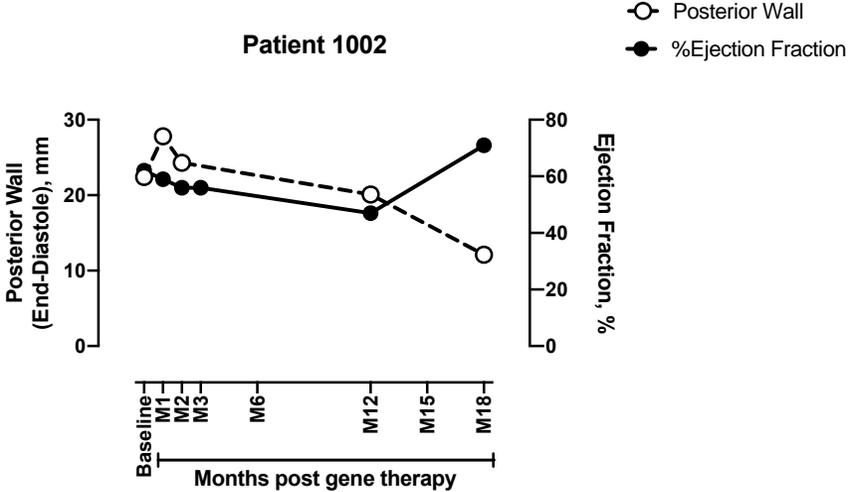
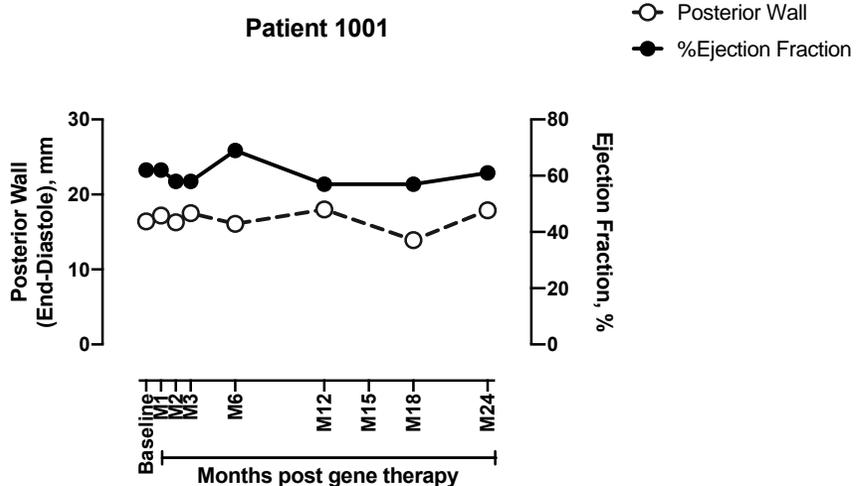
# Remodeling of Ventricular Hypertrophy on Echocardiography



All echocardiographic parameters from local laboratory assessment, conducted by a single reader



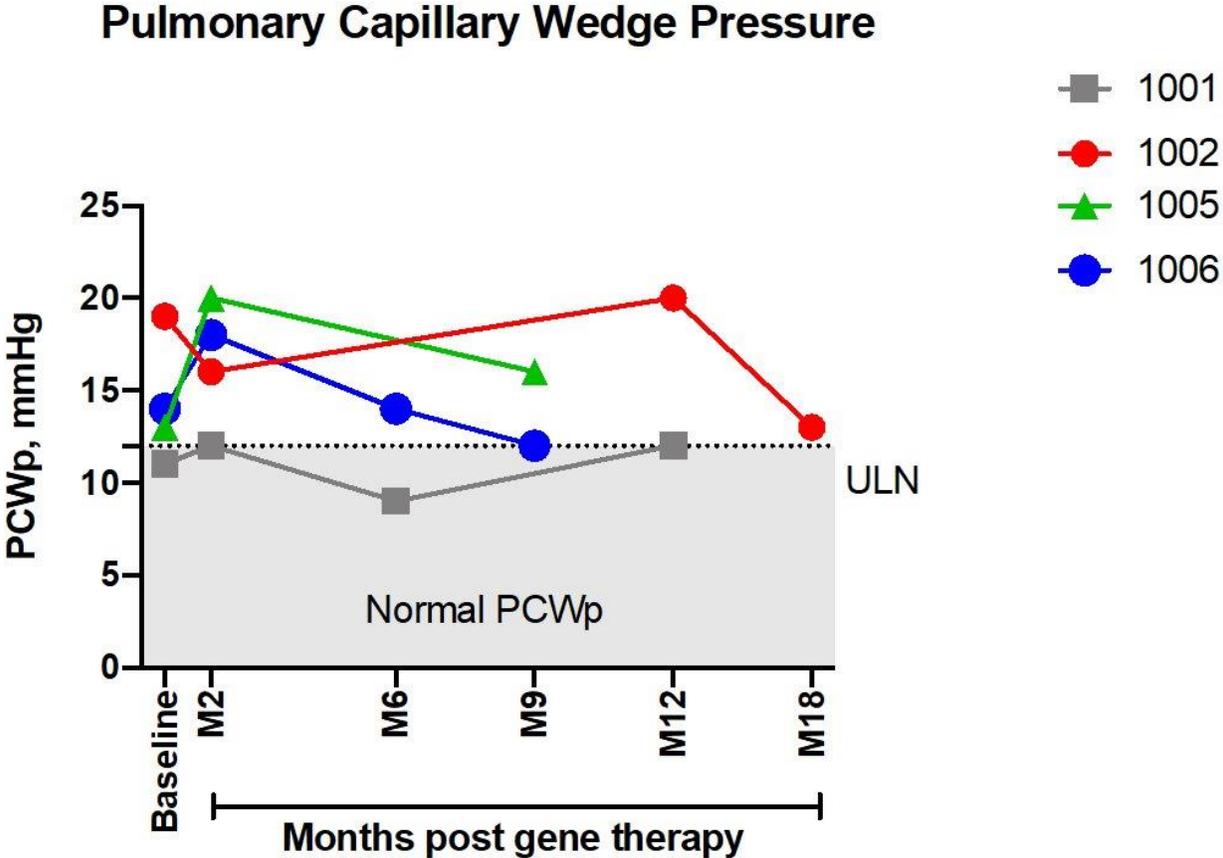
# Stabilization or Improvement of LV EF and Wall Thickness



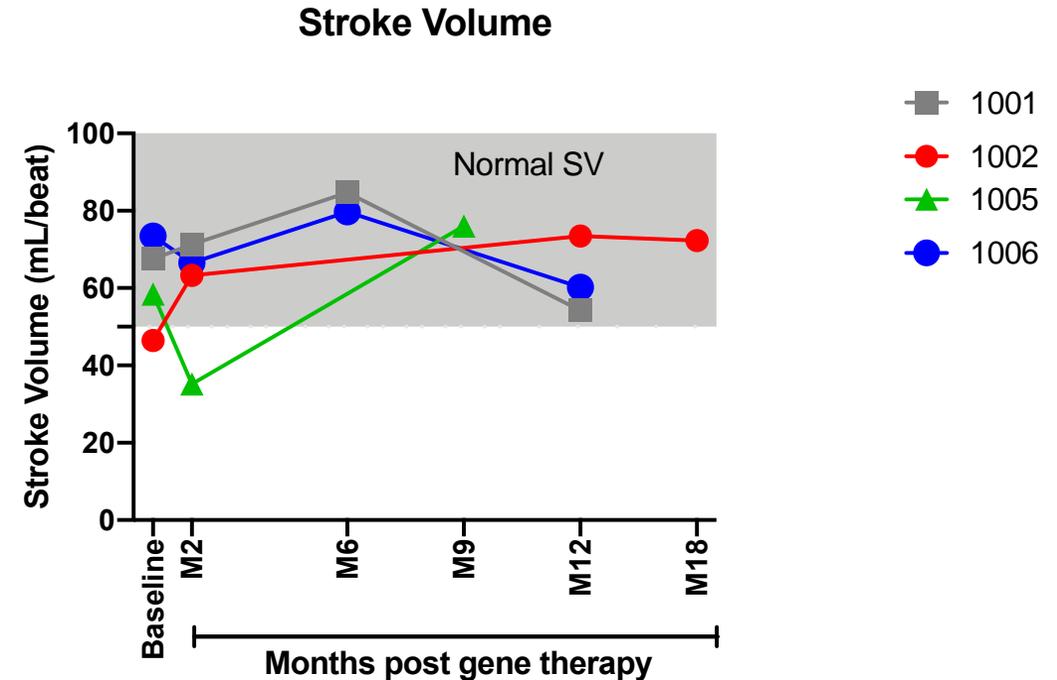
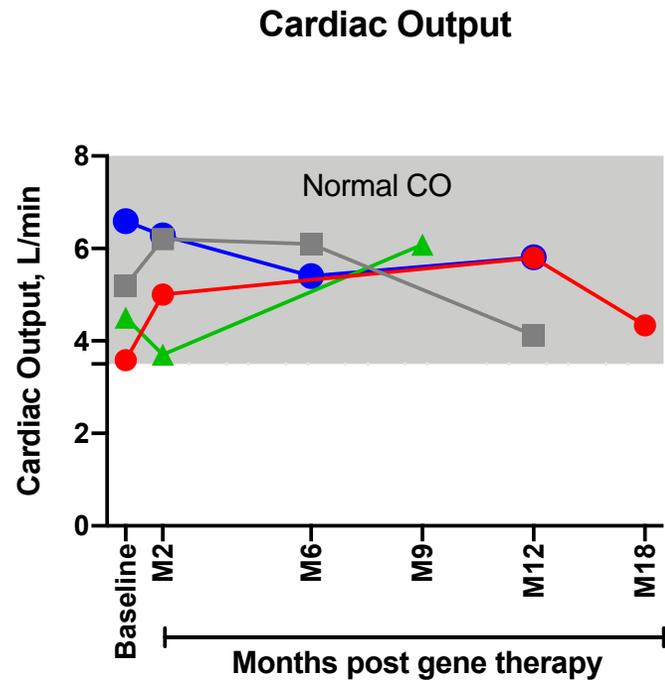
All echocardiographic parameters from local laboratory assessment, conducted by a single reader



# Invasive Hemodynamics Demonstrated Long Term Stabilization or Improvement of Diastolic Dysfunction (LV Filling Pressure)



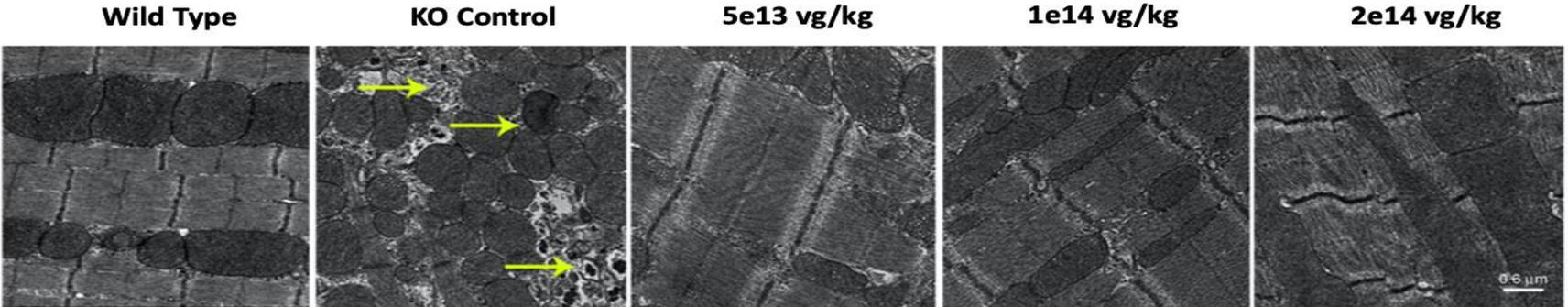
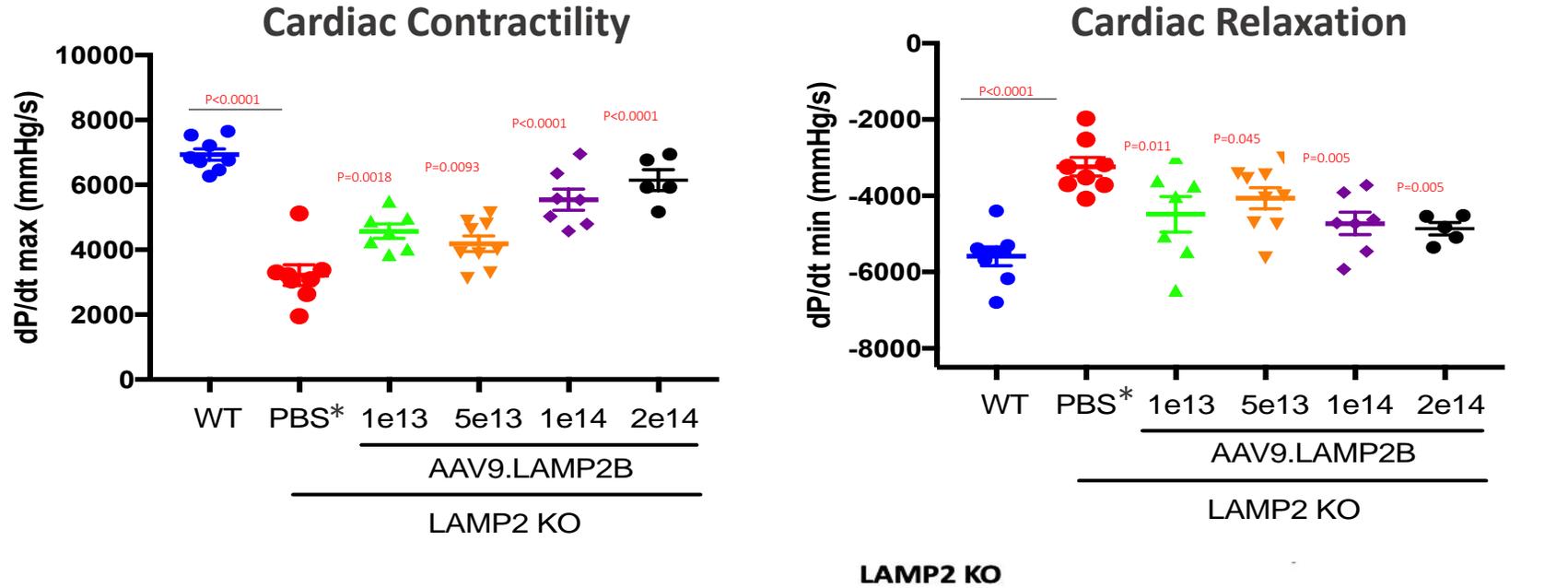
# Hemodynamic Stabilization of Systolic Function



**Cardiac Output = Stroke Volume x Heart Rate**



# RP-A501: Clinical Data Parallels Improvement Shown in Murine KO Model



Manso et al. Science Tran Med 2020



# RP-A501 Demonstrated Stable Cardiac Vector Copy Numbers (VCN)

| Cohort            | Patient ID | Cardiac VCN |  |
|-------------------|------------|-------------|--|
|                   |            | Week 8      | Month 12                                       |
| Adult - Low Dose  | 1001*      | 0.5         | 0.6  |
|                   | 1002       | 6.5         | 1.5  |
|                   | 1005       | 2.5         | 1.9 <sup>1</sup>                               |
| Adult - High Dose | 1006       | 3.9         | 1.1  |
|                   | 1007       | 5.9         | 6.8 (RV) <sup>2</sup><br>9.2 (LV) <sup>2</sup> |

<sup>1</sup> Month 9 data

<sup>2</sup> Explanted heart samples at Month 5

\* Patient 1001 was only locally monitored for compliance for two weeks; longer compliance monitoring initiated after 1001  
VCN=Vector Copies per diploid nucleus



# Endomyocardial LAMP2B Protein Expression by Immunohistochemistry (IHC)

| Cohort            | Patient ID | LAMP2B Protein Expression (by IHC)** |  |
|-------------------|------------|--------------------------------------|--|
|                   |            | Week 8                               | Month 12                               |
| Adult - Low Dose  | 1001*      | 7.3%                                 | 2.5%<br>(Previously <15%) <sup>1</sup> |
|                   | 1002       | 36.9%                                | 67.8%                                  |
|                   | 1005       | 17.6%                                | 92.4% <sup>2</sup>                     |
| Adult - High Dose | 1006       | 5.0%                                 | 100%                                   |
|                   | 1007       | 6.9%                                 | 100% <sup>3</sup>                      |

<sup>1</sup> Previously disclosed as a range due to high variance, now clarified

<sup>2</sup> Month 9 data

<sup>3</sup> Explant sample at Month 5

\* Patient 1001 was only locally monitored for compliance for two weeks; longer compliance monitoring initiated after 1001

\*\* Endomyocardial biopsies stained for LAMP2 compared to normal control samples. Percent area of cell staining was quantitated using software in a blinded fashion from 2 to 14 sections. Qualitative assessment reported for samples with high variance.



# Endomyocardial LAMP2B Western Blot Protein Expression

| Cohort            | Patient ID | LAMP2B Protein Expression<br>(by Western Blot) |  |
|-------------------|------------|--|--|
|                   |            | Week 8   | Month 5-18                                       |
| Adult - Low Dose  | 1001       | 20.7%  | 17.9% <sup>1</sup>                               |
|                   | 1002       | 27.3%  | 21.2% <sup>2</sup>                               |
|                   | 1005       | 42.8%  | 61.1% <sup>3</sup>                               |
| Adult – High Dose | 1006       | 14.6%  | 18.2% <sup>1</sup>                               |
|                   | 1007       | 25.0%  | RV: 45.1% <sup>4</sup><br>LV: 44.0% <sup>4</sup> |

<sup>1</sup> Month 6 data; inadequate sample at Month 12

<sup>2</sup> Month 18 data; inadequate sample at Month 12

<sup>3</sup> Month 9 data

<sup>4</sup> Explanted heart; Month 5 data



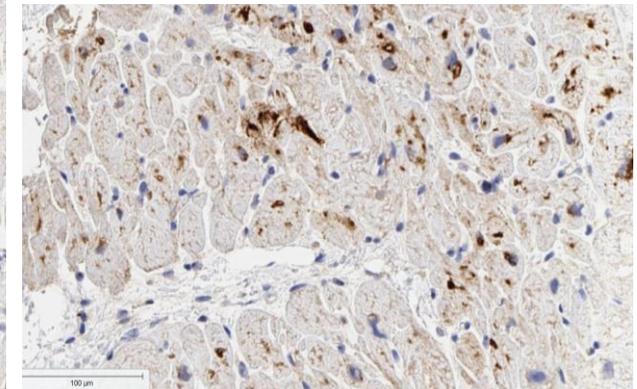
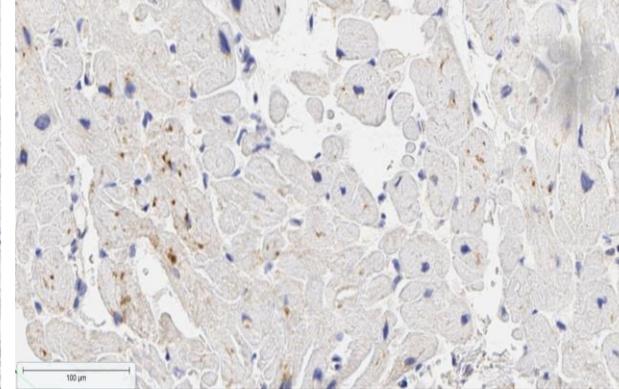
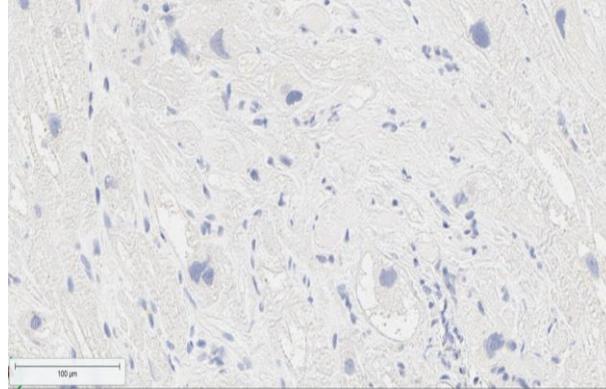
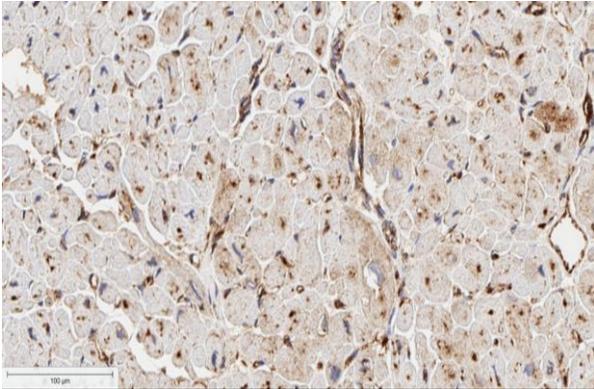
# RP-A501 Low Dose: LAMP2 Protein Expression by Immunohistochemistry and Cell Morphology by Electron Microscopy

Normal Control

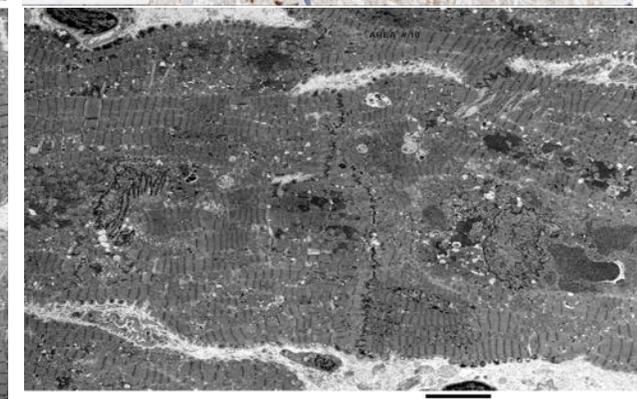
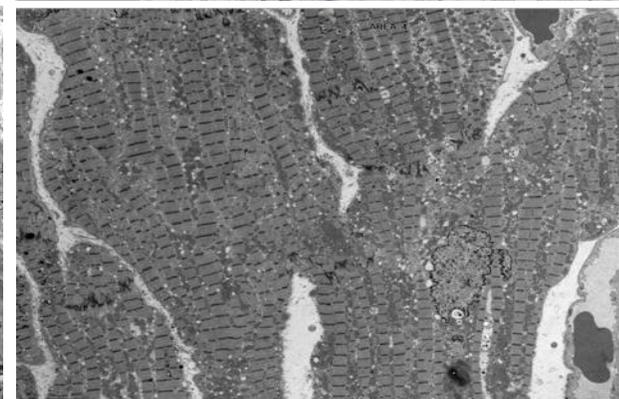
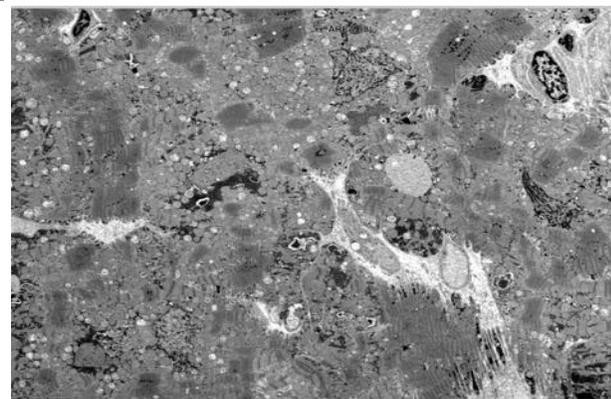
Baseline

Week 8

Month 9



Immunohistochemistry



Electron Microscopy

Representative images from patient 1005 from biopsy of IVS



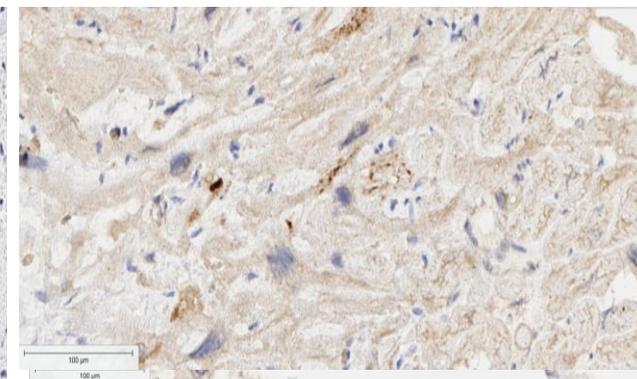
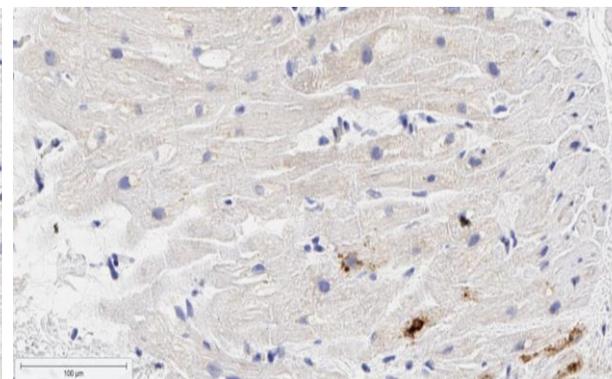
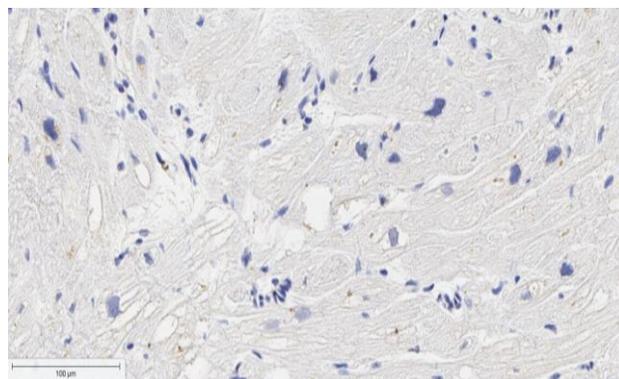
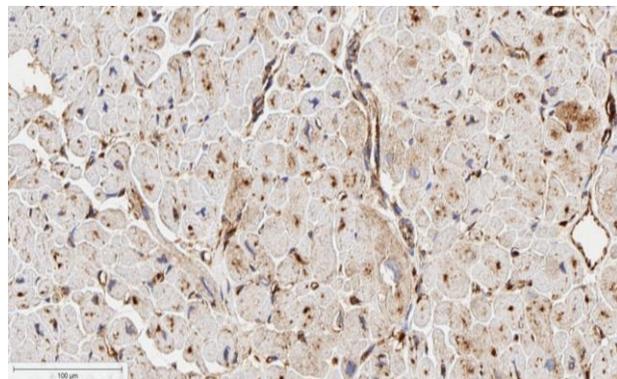
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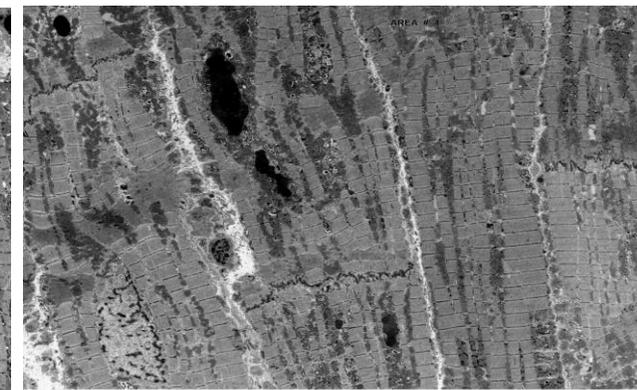
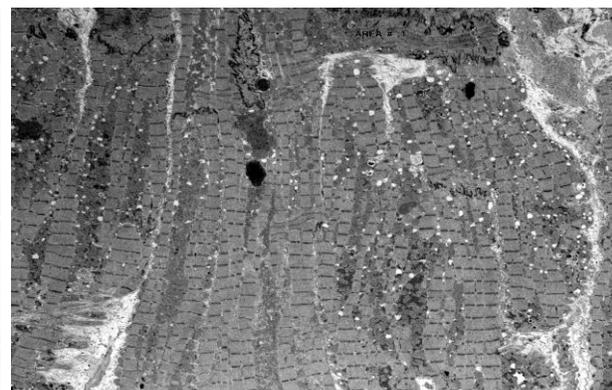
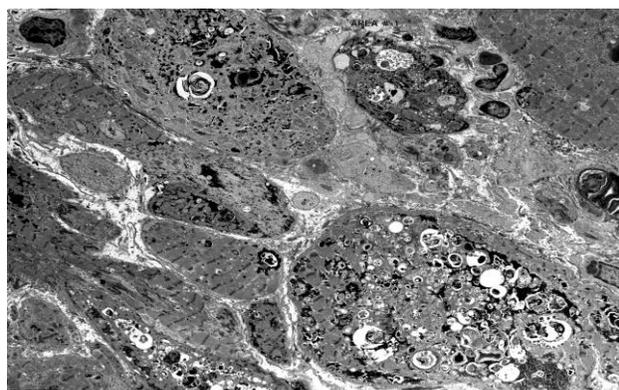
Baseline

Week 8

Month 12



Immunohistochemistry

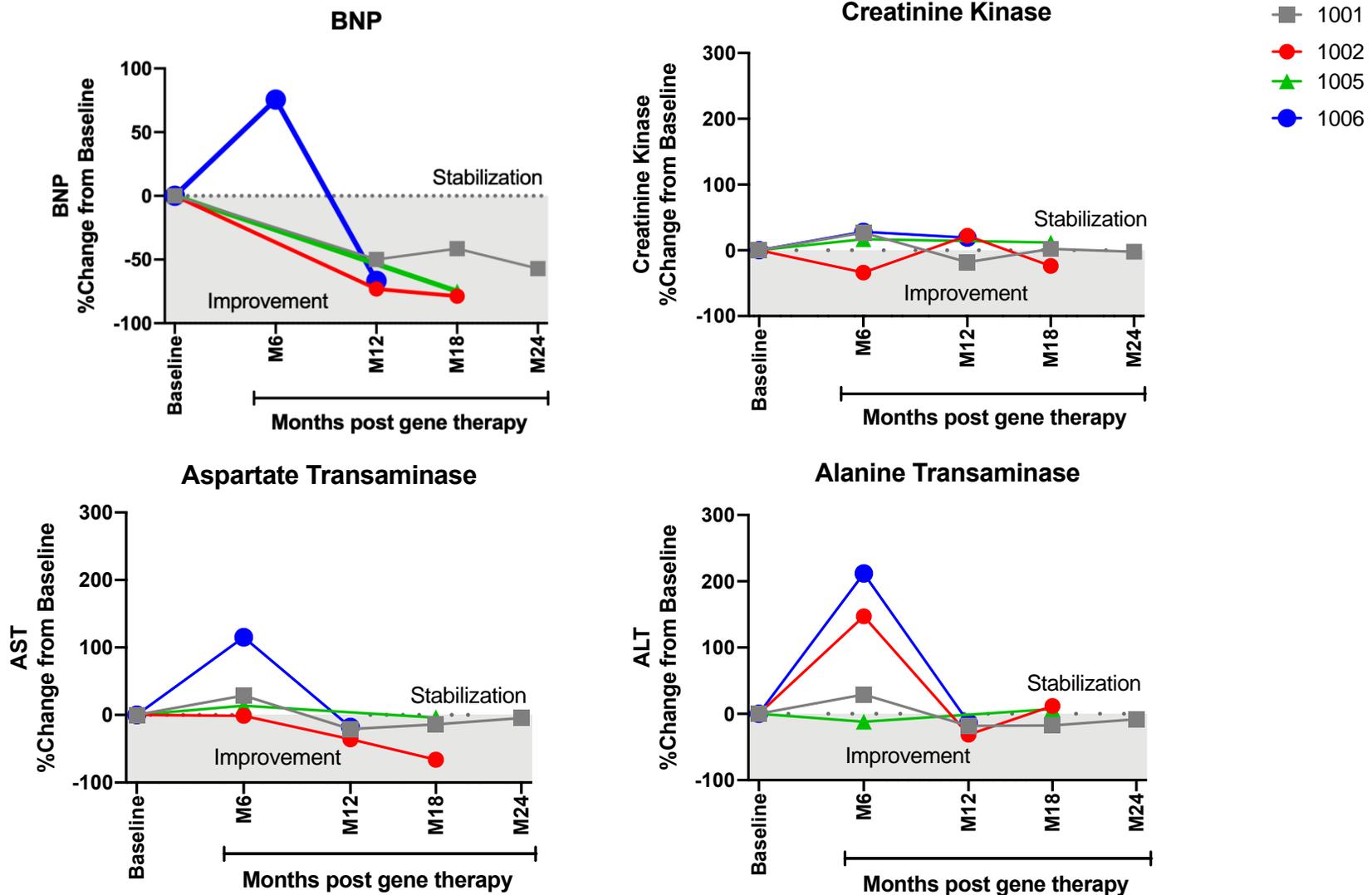


Electron Microscopy

Representative images from patient 1006 from biopsy of IVS



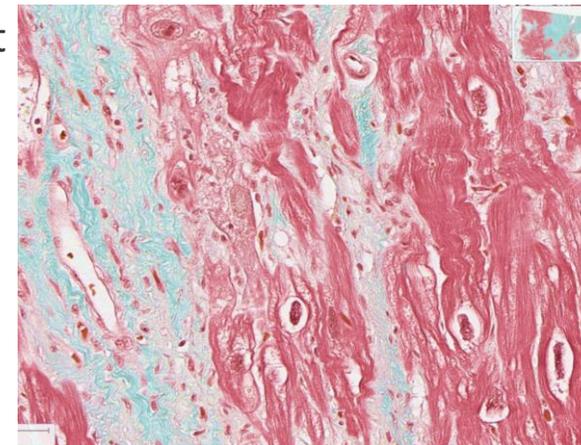
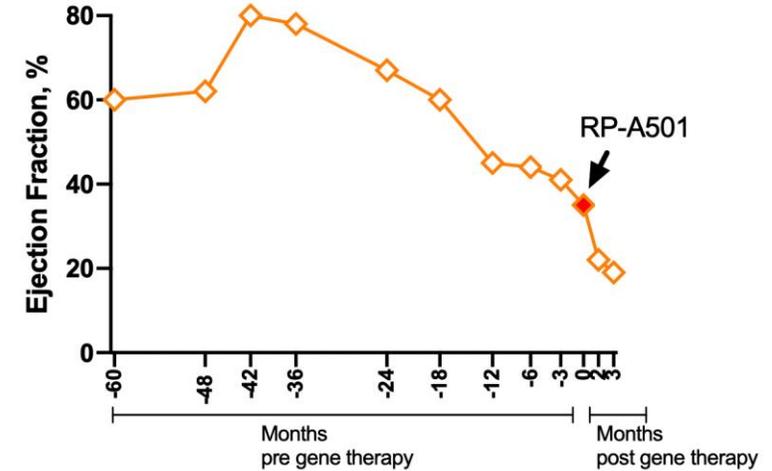
# RP-A501: Stable or Improved Clinical Biomarkers



# RP-A501 High Dose: Patient 1007 Danon Disease Progression

## 20 Year-old Male Danon Patient

- Baseline risk factors suggest "point of no return" in Danon disease progression
  - Diminished LV EF (35%)
  - Markedly elevated LV filling pressure (PCWp 26 mmHg)
  - Prior evidence of fibrosis on MRI
- Continued cardiac Danon disease progression
  - LV EF continued to decrease
  - Increased frequency of ventricular arrhythmias
- Uncontrolled arrhythmias resulting in decompensated heart failure
  - Heart transplant (Month 5)
- Danon Disease progression determined as primary cause



Trichrome Stain of Explanted LV

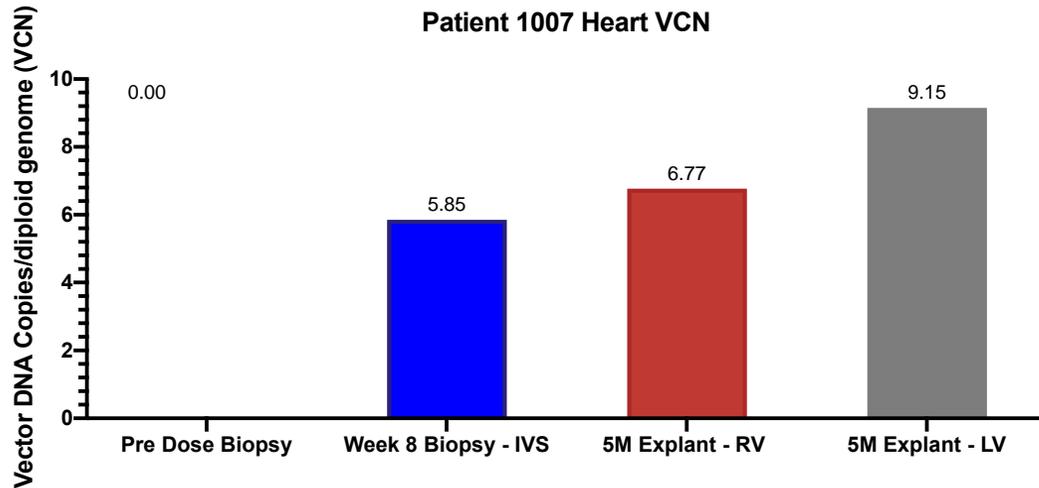
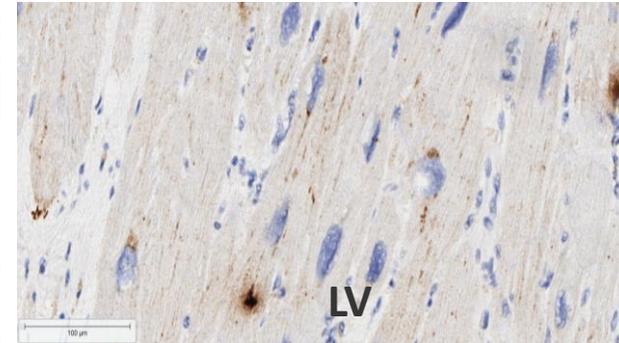
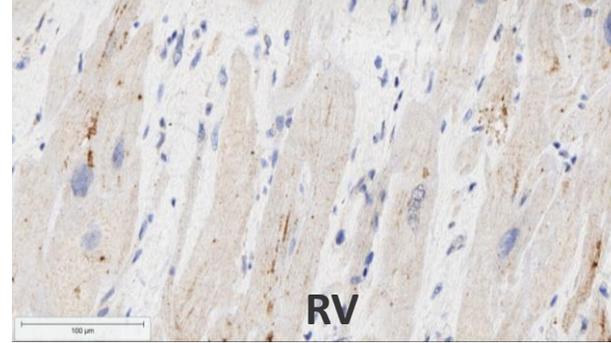
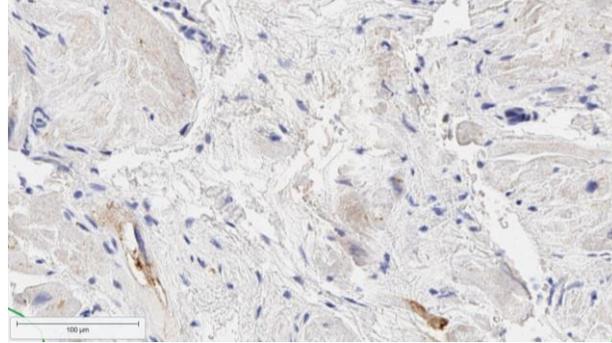
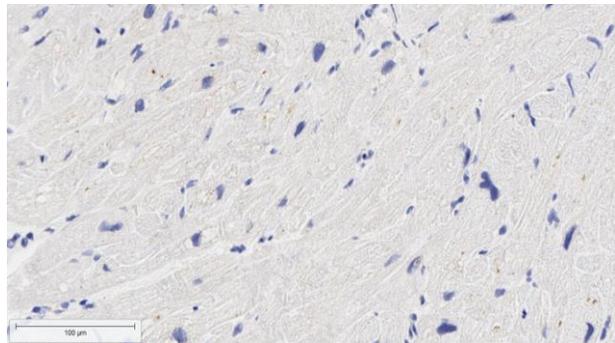
- Severe fibrosis
- No evidence of inflammation

# Patient 1007 Predose and Explanted Heart Myocardial Tissue\*

Pre-Dose Biopsy (IVS)

Week 8 Biopsy (IVS)

Explanted Heart – 5M post treatment



| Patient ID | LAMP2B Protein Expression (by IHC) |                    |                    |
|------------|------------------------------------|--------------------|--------------------|
|            | Week 8                             | Month 5 Explant RV | Month 5 Explant LV |
| 1007       | 6.8%                               | 100%               | 100%               |

\* Atrial VCN and LAMP2 expression was consistent with ventricular expression (100%)

IHC = Immunohistochemistry



# RP-A501 High Dose Adult and Adolescent Cohort

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- **RP-A501 r-AAV dose-dependent toxicity was seen at  $1.1 \times 10^{14}$  GC/kg dose levels**
  - One of two patients developed thrombotic microangiopathy (TMA)
    - Acute renal failure managed with hemodialysis and eculizumab
    - Baseline LV systolic failure may have contributed
    - Largest patient in clinical trial (>90kg) who received highest total dose ( $1.06 \times 10^{16}$  GC)
- **Histologic evidence of LAMP2B gene expression that is sustained**
  - Cellular level (explanted heart)
    - Robust expression in key target areas of heart (ventricles)
    - Improved LAMP2B protein expression
    - Higher expression relative to endomyocardial biopsies (EMB)

**Clinical parameters improved or remained stable (comparable to low dose cohort) in high dose patient treated before end-stage Danon disease (1006)**



# RP-A501 Low Dose Adult and Adolescent Cohort

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RP-A501 r-AAV generally well tolerated at  $6.7 \times 10^{13}$  GC/kg dose level

- Tailored immunosuppressive regimen
- Reversible immunologic response with no lasting clinical sequelae

## Clinical parameters improved or remained stable

- Functional and Biomarker Parameters
  - NYHA class improved or stabilized
  - 6-minute walk distance mildly improved or stabilized
  - BNP decreased or stabilized
- Echocardiograph Parameters
  - LV wall thickness decreased or stabilized
  - Improved or stable ejection fraction by 12 months
- Hemodynamic Parameters
  - Cardiac output remained normal with stable or improved left heart filling pressures (Pulmonary wedge)

## Histologic evidence of LAMP2B gene expression that is sustained

- Stable and robust LAMP2B protein expression
- Decreased vacuoles and improved architecture on electron microscopy



# The Impact of the Clinical Trial from Parents of Danon Patients

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“Prior to [my son] receiving this therapy he could barely walk up a flight of stairs without having to stop and catch his breath. He stayed in his room playing video games only to go outside when he had school or to ride his motorized scooter in the neighborhood or at school. He complained of fast heart rates and chest pain often. He would tire easily and not want to go many places.” Eighteen months later, he **“is stronger than I’ve ever seen. He can walk upstairs without being short of breath or having to stop half-way. He doesn’t have chest pain or fast heart rates like he used too [...] about 4 months after his therapy trial he started working and stopped using his motorized scooter all together [...] He is now able to work 4-6 hours a day standing, driving and sitting.** I know this wouldn’t be possible without the gene therapy he received. I [...] know with time he will only continue to be able to do more of the things that other kids his age can do.”

“Our son was diagnosed with Danon disease [at] 9 years old. We had never heard of the disease and what we learned as we tried to find information on the internet was devastating [...] he took it hard. He worried so much about his future without telling us [...] we understood he would become much sicker in his twenties [...] we hoped science and research would help him within the next 10 years [...] [He] normally object to all new things, wanted to join as soon as he heard about [the trial]. [He said] 'I don’t want to die young'. **[W]e see him smile more now, he makes plans for moving to his own place and working a couple of days a week [...] We see him much more positive and relaxed. He has a possibility to become better, he feels better, and he didn’t think that would ever happen.”**



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