Update from Phase 1 Trial of RP-A501 Gene Therapy Treatment for Danon Disease

September 30, 2022

DISCLAIMER

Various statements in this release concerning Rocket's future expectations, plans and prospects, including without limitation, Rocket's expectations regarding its guidance for 2022, the safety and effectiveness of RP-A501 for the potential treatment of Danon Disease, trends for RP-A501 safety and efficacy based on the adult patients treated to date, the expected timing and outcome of Rocket's regulatory interactions and planned submissions, including in connection with the potential advancement toward a Phase 2 pivotal study for RP-A501, Rocket's plans for the advancement of its Danon Disease program and the safety, effectiveness and timing of related pre-clinical studies and clinical trials, may constitute forward-looking statements for the purposes of the safe harbor provisions under the Private Securities Litigation Reform Act of 1995 and other federal securities laws and are subject to substantial risks, uncertainties and assumptions. You should not place reliance on these forward-looking statements, which often include words such as "believe," "expect," "anticipate," "intend," "plan," "will give," "estimate," "seek," "will," "may," "suggest" or similar terms, variations of such terms or the negative of those terms. Although Rocket believes that the expectations reflected in the forward-looking statements are reasonable, Rocket cannot guarantee such outcomes. Actual results may differ materially from those indicated by these forward-looking statements as a result of various important factors, including, without limitation, Rocket's ability to monitor the impact of COVID-19 on its business operations and take steps to ensure the safety of patients, families and employees, the interest from patients and families for participation in each of Rocket's ongoing trials, our expectations regarding the delays and impact of COVID-19 on clinical sites, patient enrollment, trial timelines and data readouts, our expectations regarding our drug supply for our ongoing and anticipated trials, actions of regulatory agencies, which may affect the initiation, timing and progress of pre-clinical studies and clinical trials of its product candidates, Rocket's dependence on third parties for development, manufacture, marketing, sales and distribution of product candidates, the outcome of litigation, and unexpected expenditures, as well as those risks more fully discussed in the section entitled "Risk Factors" in Rocket's Annual Report on Form 10-K for the year ended December 31, 2021, filed February 28, 2022 with the SEC and subsequent filings with the SEC including our Quarterly Reports on Form 10-Q. Accordingly, you should not place undue reliance on these forward-looking statements. All such statements speak only as of the date made, and Rocket undertakes no obligation to update or revise publicly any forward-looking statements, whether as a result of new information, future events or otherwise.

Danon Disease (DD): Serious Condition with Unmet Medical Need

Disease Etiology

- X-linked, dominant, monogenic disease
- Loss-of-function mutations in *LAMP-2B*

Therapeutic Challenges

- Standard of care:
  - Heart transplant (HTx)
- Limitations:
  - Considerable morbidity and mortality
  - Only ~20% of patients receive HTx
  - Not curative of extracardiac disease

Clinical Manifestations

Impaired autophagy

- Prominent autophagic vacuoles
- Myocardial disarray

Other clinical manifestations

- Skeletal myopathy
- CNS manifestations
- Ophthalmologic manifestations

Severe cardiomyopathy

- Mortality secondary to heart failure or arrhythmia
- Males: Aggressive disease course, median overall survival: 19 years
- Females: Delayed median presentation (~20 years later) due to additional X chromosome, highly morbid and fatal disorder

Addressable Market (US & EU)

Prevalence of **15,000 to 30,000** individuals
Annual incidence of **800 to 1,200** individuals

CNS, central nervous system; LAMP-2B, lysosome-associated membrane protein 2B.

Boucek D et al. *Genet Med.* 2011;13(6):563-568. Brambatti M et al. *Int J Cardiol.* 2019;286:92-98.

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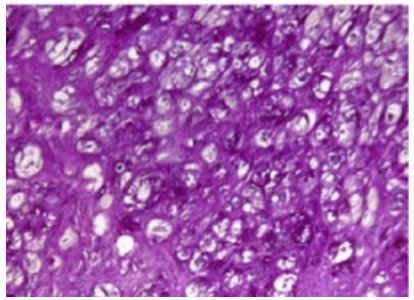
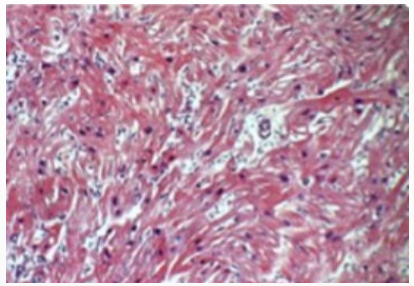
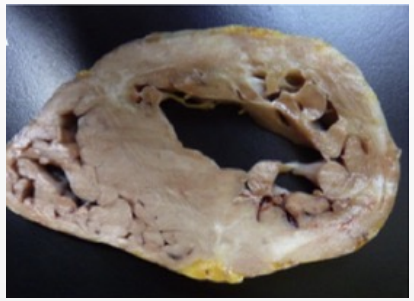
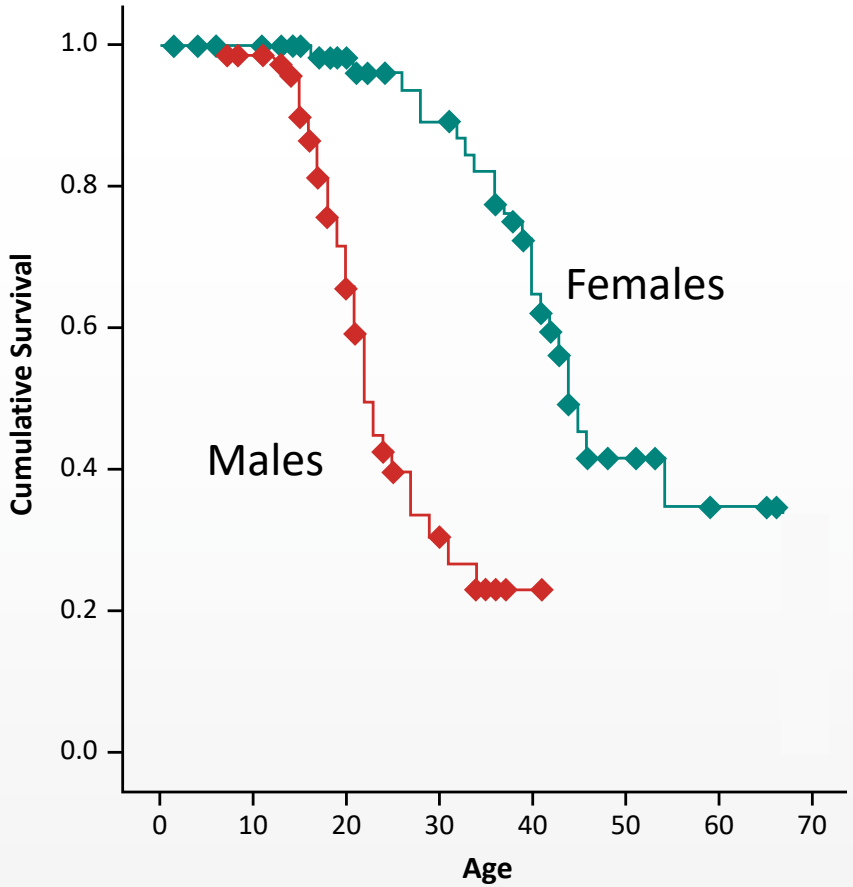
Heart Transplant is the Current Standard of Care, But Is Not Curative of DD









Lysosomal Associated Membrane Protein 2B (*LAMP2B*) Mutation Causes DD

- **Cardiac histology**
  - Absence of LAMP2 immunostaining
  - Prominent accumulation of autophagic vacuoles
  - Myocardial disarray
  - Myocardial hypertrophy

Cardiac Manifestations

- **Males**:
  - HCM (>95%) with arrhythmias
  - Mortality in 2nd to 3rd decade of life
- **Females:**
  - Dilated/hypertrophic CM and arrhythmias
  - Mortality in 4th to 5th decade of life

Cardiac Mortality

- Mortality secondary to heart failure
- Cardiac defibrillator is not life-saving
- Heart transplant, when available, is associated with high morbidity and mortality

CM, cardiomyopathy; CNS, central nervous system; *LAMP-2B*, lysosome-associated membrane protein 2B.
Boucek D, Jirikowic J, Taylor M. Genet Med 2011; 13(6):563-68. Image from Bottillo I, et al. Cardiovasc Pathol. 2016;25(5):423-31.

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RP-A501: Prospect of Direct Benefit

Trajectory of cardiac pathophysiology and heart failure in male Danon disease patients

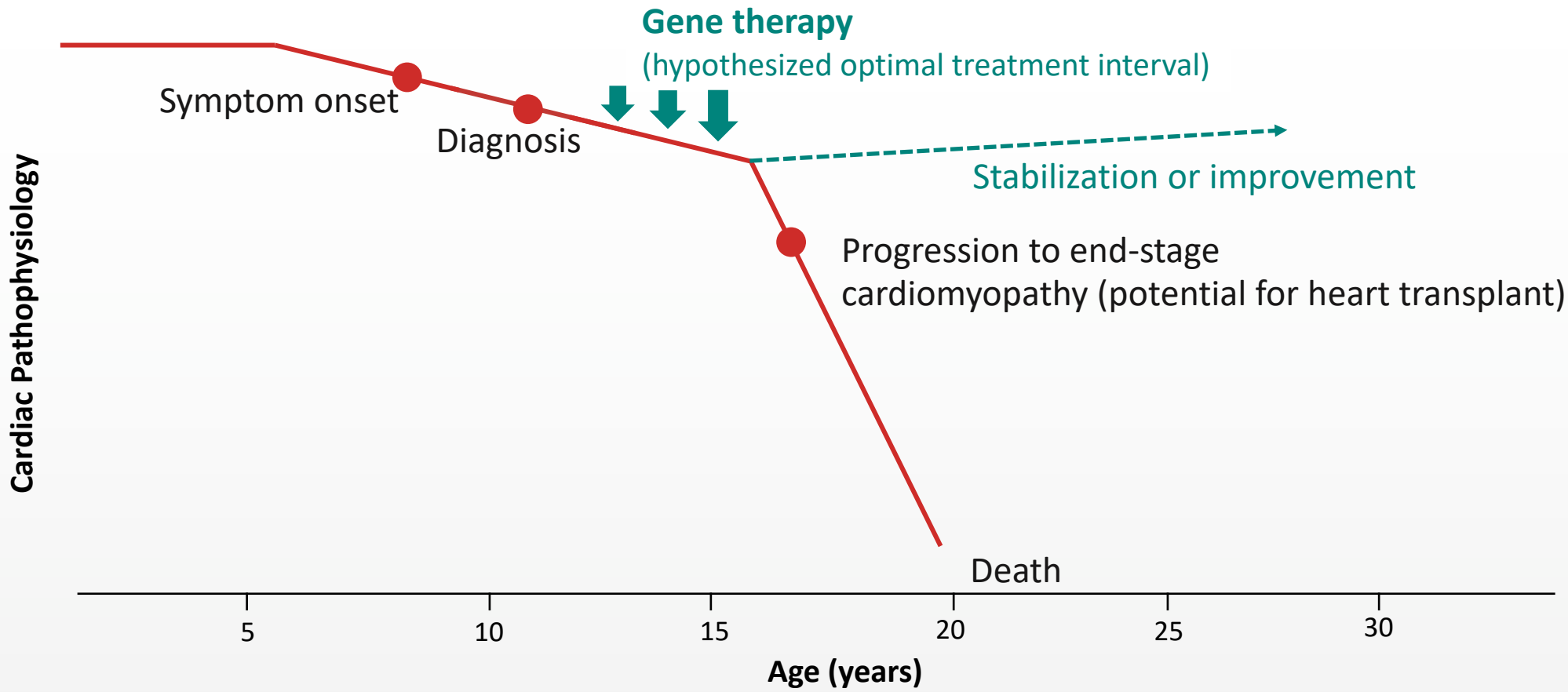
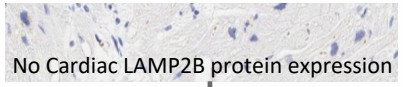


Figure modified from disease progression by age data from Boucek D et al. *Genet Med.* 2011;13(6):563-568 and Brambatti M et al. *Int J Cardiol.* 2019;286:92-98.

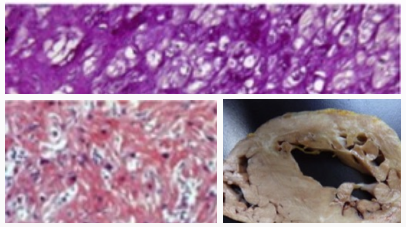
Pathophysiology and Clinical Manifestations of Danon Disease HCM

Pathophysiology

Pathogenic *LAMP-2B* mutation causing DD

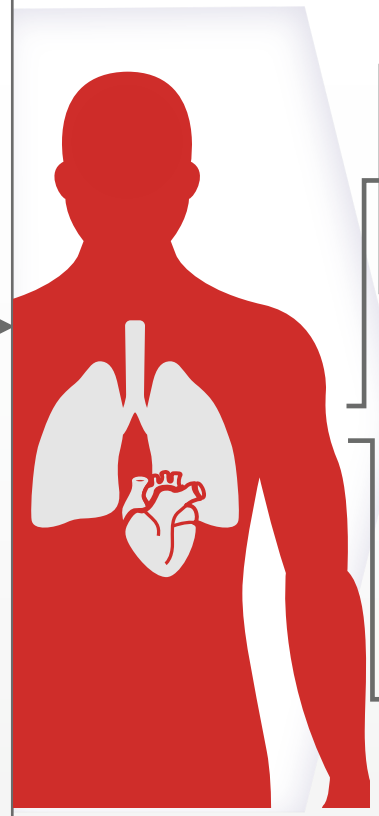


Autophagic vacuoles, myocardial disarray, myocardial thickening



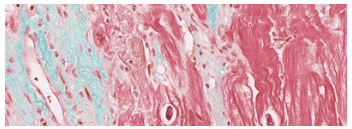
Impaired ventricular filling during diastole (diastolic dysfunction)

Mechanism



Disorganized myocytes disrupt signal conduction → Ventricular arrhythmias

Microvascular ischemia, apoptosis with fibrous substitution → Fibrosis



Fibrosis → Impaired systolic function

Decreased cardiac output

↓ Coronary artery perfusion, mismatch of myocardial oxygen supply & demand → Myocardial injury → Impaired systolic function

Tissue hypoxia → Stimulus to breathe

↑ Left-sided pressure → Pulmonary edema and ↑ work of breathing

Patient impact

- Sudden cardiac arrest
- End-Stage Heart Failure
- Fatigue
- Tachypnea
- Dyspnea on exertion

DD, Danon disease; LAMP2B, lysosome-associated membrane protein 2B; VT, ventricular tachycardia.
Adapted from Jones & Arnold. 2014. Hypertrophic Cardiomyopathy: Pathogenesis and Clinical Findings

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Summary of Results and Conclusions

Phase 1 enrollment and treatment are **complete**

- ✓ The enhanced immunomodulatory regimen **was well tolerated and has effectively mitigated adverse events** in the pediatric cohort, who are currently 6 to 11 months post treatment
- ✓ The **early LAMP2 expression data from the pediatric cohort are encouraging and consistent** with that seen in the adult patients at the same timepoints
- ✓ The **early clinical trends for the pediatric cohort are encouraging and consistent** with the **sustained clinical responses seen in the adults at 24-36 months**
- ✓ **Study design and endpoints have been identified** for the planned Phase 2 pivotal study* and **endorsed by an International Scientific and Clinical Advisory Board**; FDA discussion planned at the end of this year

*Pending regulatory feedback

Safety and Efficacy Data from the First Pediatric Cardiomyopathy Gene Therapy Trial: RP-A501 (AAV9:LAMP2B) for Danon Disease

Phase 1 Study: Non-Randomized Open Label

Non-randomized open label study in male DD patients

INCLUSION CRITERIA

- Male
- Confirmed *LAMP-2B* mutation
- Cardiac involvement confirmed by imaging or ECG
- NYHA Class II or III
- Able to walk >150 m 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 pediatric cohort)

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

Pediatric
8-14 years
n=2 at CHOP

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

Low Dose:
6.7×10^{13} GC/kg

High Dose*:
1.1×10^{14} GC/kg
*No further enrollment at this dose.

Enrollment Complete

36 months

PRIMARY OUTCOMES

- **Early and long-term safety**
- Target tissue transduction & LAMP2B protein expression
- Improved myocardial histology
- Clinical improvement or stabilization

Data Reporting Details

- Pre-dose (baseline) value defined as the mean values from all visits prior to infusion
- Core lab data presented for echocardiographic parameters, cardiac serologies, and cardiac histology
- Data cut September 27, 2022; source data verification through July 11, 2022.

6MWT, 6-minute walk test; AAV, adeno-associated virus; CHOP, Children's Hospital of Philadelphia; DD, Danon disease; ECG, electrocardiogram; *LAMP-2B*, lysosome-associated membrane protein 2B; LVEF, left ventricle ejection fraction; NYHA, New York Heart Association; UCSD, University of California San Diego.

RP-A501: Safety Monitoring of Phase 1 Patients

Cohort 1: Low-dose adult

Pt	Age	Wt
1001[a]	17.5	52.5
1002	20.4	89.1
1005	18.3	91.8

RP-A501 6.7 x 10^{13} GC/kg

Steroid (prednisone 1mg/kg)

Tacrolimus

SAEs of Interest
n=2 grade 3 steroid myopathy

Platelets
n=2, Grade 1 decrease (to LLN range)

Cohort 2: High-dose adult

Pt	Age	Wt
1006	21.1	82.7
1007[b]	20.7	96.7

RP-A501 1.1 x 10^{14} GC/kg

Steroid (prednisone 1mg/kg)

Tacrolimus

Rituximab (2 doses)

n=1 grade 4 TMA
n=1 grade 3 steroid myopathy

n=1, Grade 4 decrease

Cohort 3: Low-dose pediatric

Pt	Age	Wt
1008	12.3	70.5
1009	11.7	55.7

RP-A501 6.7 x 10^{13} GC/kg

Daily, real-time monitoring of labs & clinical status

Day -14 | Day 14 | Month 3

Steroid (prednisone 0.5 – 0.8mg/kg); Taper start d 10

Sirolimus (target trough 4-8 ng/mL)

Rituximab (2 doses)

none

Remain in normal range

[a] Corticosteroid compliance uncertain
[b] This patient underwent heart transplant due to DD progression five months post RP-A501 infusion; both because this patient would no longer be eligible for future studies based on revised eligibility criteria and because long-term RP-A501 effect is not evaluable, data for this patient are not shown. He is currently stable.

d, day; LLN, lower limit of normal; Pt, patient; SAE, serious adverse event; TMA, thrombotic microangiopathy; Wt, weight.
Age in years at RP-A501 infusion; weight in kg.

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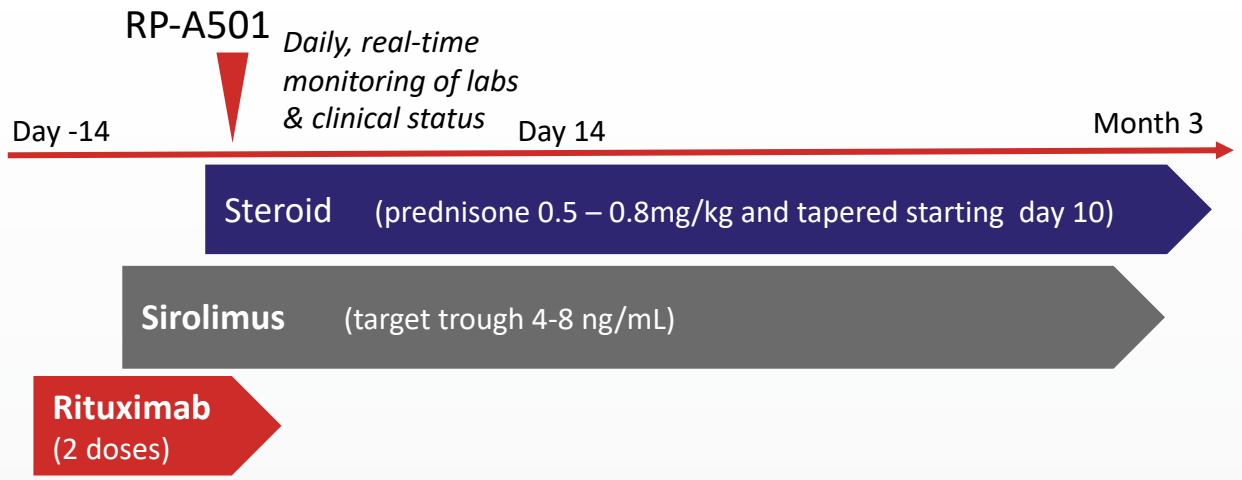
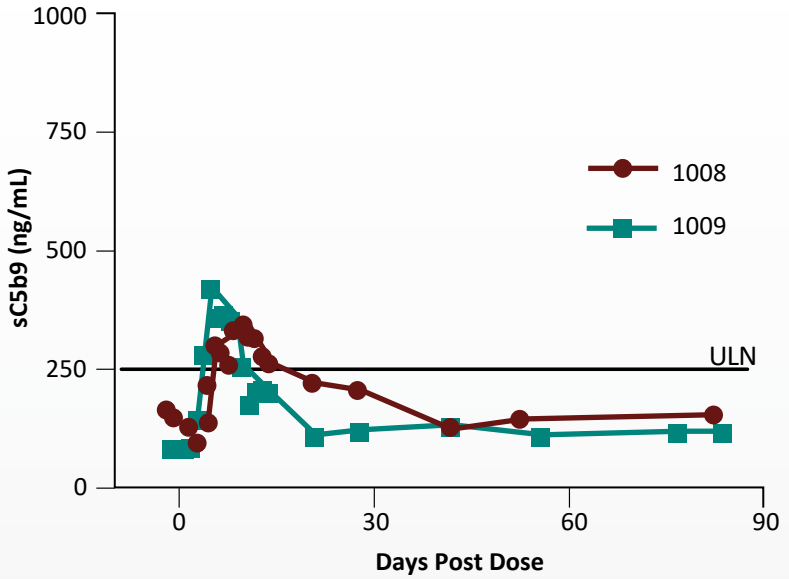
RP-A501 Was Generally Well Tolerated in Pediatric Cohort on Enhanced Immunomodulation

All AEs were Transient and Reversible with 6 and 11 month follow up in 1008 and 1009, respectively

Pediatric immunomodulation protocol



sC5b9 Evaluation Post RP-A501



Platelets remained within normal range

No reported **skeletal myopathy or late transaminitis** with initial steroid dose-reduction and more rapid taper, and introduction of sirolimus

- **Minimal complement activation**
- **No complement-related clinical or laboratory AEs**
- **All AEs were transient and reversible**
- **No treatment-related SAEs**

AE, adverse event; SAE, serious AE; ULN, upper limit of normal.
Data cut-off September 27, 2022 with source data verification through July 11, 2022.

Early Pediatric Data are Encouraging and Consistent with Adult Efficacy

Patient ID: A501-008-1008

Baseline Characteristics

AGE AT INFUSION
12.3 years

ICD yes[1]

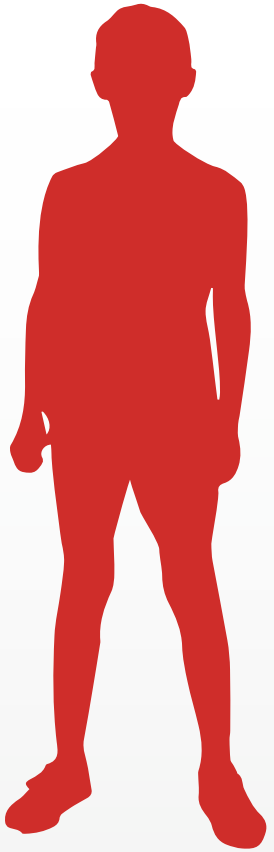
WPW yes

MAX LV WALL THICKNESS
41.9 mm, z-score +32

6MWT
438 meters

9 months

Variable	Baseline[2]	Most Recent Follow-up
LAMP2 protein[3] (%)	0.5	21[4]
Troponin-I (ng/mL)	1.89	0.28
BNP (pg/mL)	1837	406
KCCQ-overall scale	50	93
NYHA Class	II	I



Patient ID: A501-008-1009

Baseline Characteristics

AGE AT INFUSION
11.7 years

ICD no

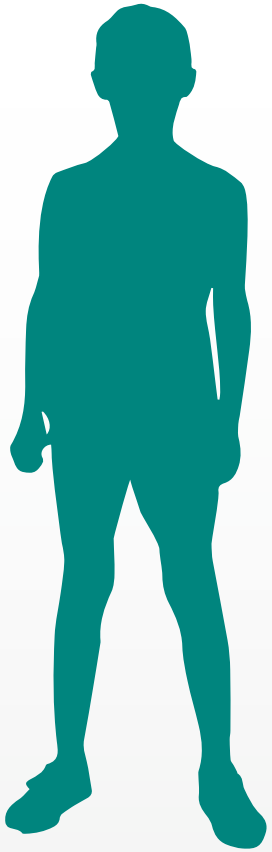
WPW no

MAX LV WALL THICKNESS
19.8 mm, z-score +12

6MWT
553 meters

6 months

Variable	Baseline[2]	Most Recent Follow-up
LAMP2 protein[3] (%)	2.6	35[4]
Troponin-I (ng/mL)	0.67	0.07
BNP (pg/mL)	297	113
KCCQ-overall scale	52	81[5]
NYHA Class	II	I



[1] Recommended prior to enrollment; ICD implanted 3 months after RP-A501 infusion
[2] Baseline values for troponin-I and BNP are the mean values from all pre-dose visits
[3] All biopsies stained for LAMP2 were compared to normal controls. Data is quantitated in a blinded fashion from ~3-5 sections
[4] Most recent biopsy data available from 6 month visit for 1008 and 3 month visit for 1009
[5] Most recent KCCQ data available from 3 month visit for 1009

6MWT, 6-minute walk test; BNP, brain natriuretic peptide; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City cardiomyopathy questionnaire; LAMP2, lysosome-associated membrane protein 2; LV, left ventricle; NYHA, New York Heart Association; WPW, Wolff-Parkinson-White syndrome.
Data cut-off September 27, 2022 with source data verification through July 11, 2022.

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Early Pediatric LAMP2 Expression are Encouraging and Consistent with Adult Data

Quantified LAMP2 protein expression by immunohistochemistry (IHC)

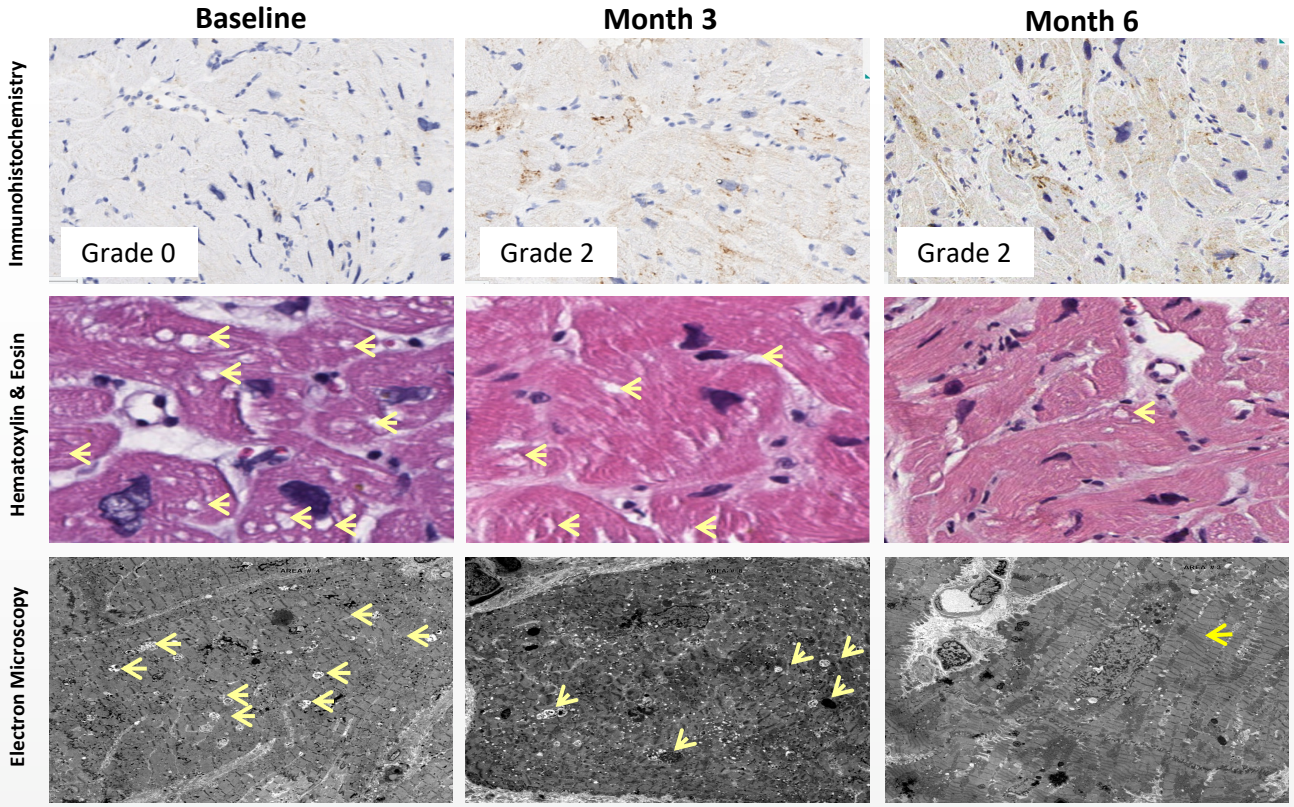
Cohort	Patient ID	Initial Biopsy Post Infusion
Pediatric - Low Dose	**1008**	*Month 3:* **18.5%***
	1009	*Month 3:* **34.7%**
Adult - Low Dose	1001	*Month 2:* 7.3%
	1002	*Month 2:* 36.9%
	1005	*Month 2:* 17.6%
Adult - High Dose	1006	*Month 2:* 5.0%
	1007	*Month 2:* 6.9%

All biopsies stained for LAMP2 were compared to normal control samples. Data is quantitated in a blinded fashion from ~3-5 sections.
* 1008 Month 6 biopsy: 21% as noted in previous slide

LAMP2, lysosome associated membrane protein 2.
IHC, immunohistochemistry.

LAMP2 Myocardial Protein Expression and Histologic Improvement in the Pediatric Cohort

A501-008-1008 Endomyocardial Biopsy (EMB) Images



LAMP2 protein expression assessed (relative to normal human controls) by core lab in a blinded fashion of entire tissue sample

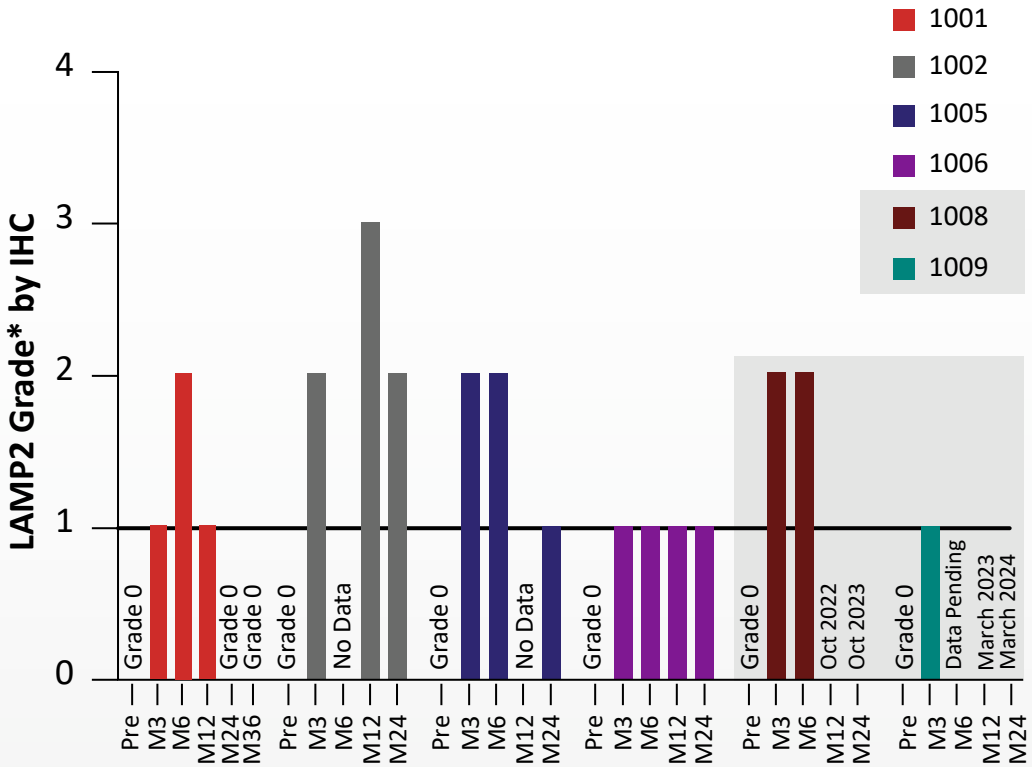
- Percentages reflect estimated extent of LAMP2 staining
  - Grade 0 negative staining
  - Grade 1 ≤25%
  - Grade 2 26%-50%
  - Grade 3 51%-75%
  - Grade 4 >75%
- H&E images captured at 20x magnification, presented digitally zoomed
- Arrows indicate autophagic vacuoles
- Similar findings on EMB from patient 1009 at Baseline and Month 3

EMB, endomyocardial biopsy; H&E, hematoxylin & eosin stain; LAMP2, lysosome associated membrane protein 2.

Extended results from Phase 1 Cardiomyopathy Gene Therapy Trial: RP-A501 (AAV9:LAMP2B) For Danon Disease

Pediatric LAMP2 Protein and DNA Suggests Durable Expression As Demonstrated in Adult Cohort

LAMP2 Protein Expression



*LAMP2 protein expression assessed (relative to normal human controls) by core lab in a blinded fashion of entire tissue sample; Percentages reflect estimated extent of LAMP2 staining: Grade 0=negative staining; Grade 1 ≤25%; Grade 2 =26%-50%; Grade 3 =51%-75%; Grade 4 >75%.

Cardiac LAMP2 DNA by qPCR (vector copies per diploid nucleus)

Patient ID	Predose	Month 6	Month 12	Month 36
1001[a]	0	0.384	0.197	0.120
1002	0	ND	0.575	0.590[c]
1005	0	0.583	ND	1.228[c]
1006	0	2.693	1.131	-
1007	0	RV: 6.77[b] LV: 9.15[b]	Post heart transplant	
1008	0	0.492	-	-
1009	0	Data pending	-	-

LV, Left ventricle and RV, Right ventricle at 5 months from explanted heart; ND. not done, -, visit pending.
[a] Corticosteroid compliance uncertain. [b] Assessment from explanted heart tissue at 5 months. [c] Month 30 visit.

LAMP2, lysosome associated membrane protein 2; M, month.

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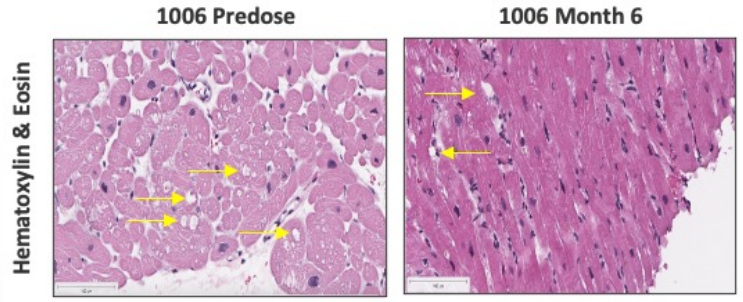
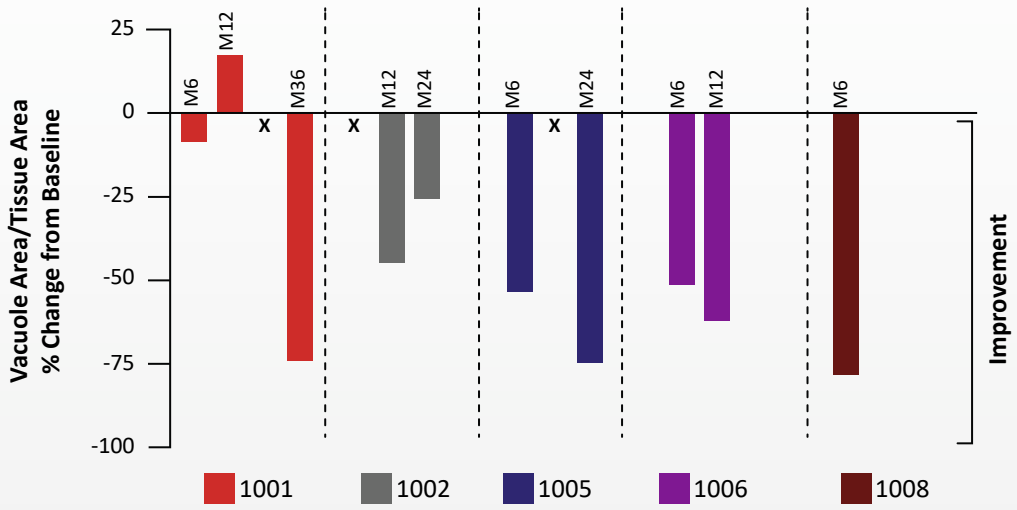
Restored Autophagy is Sustained Following RP-A501

Restored autophagy indicated by attenuation of vacuolar area

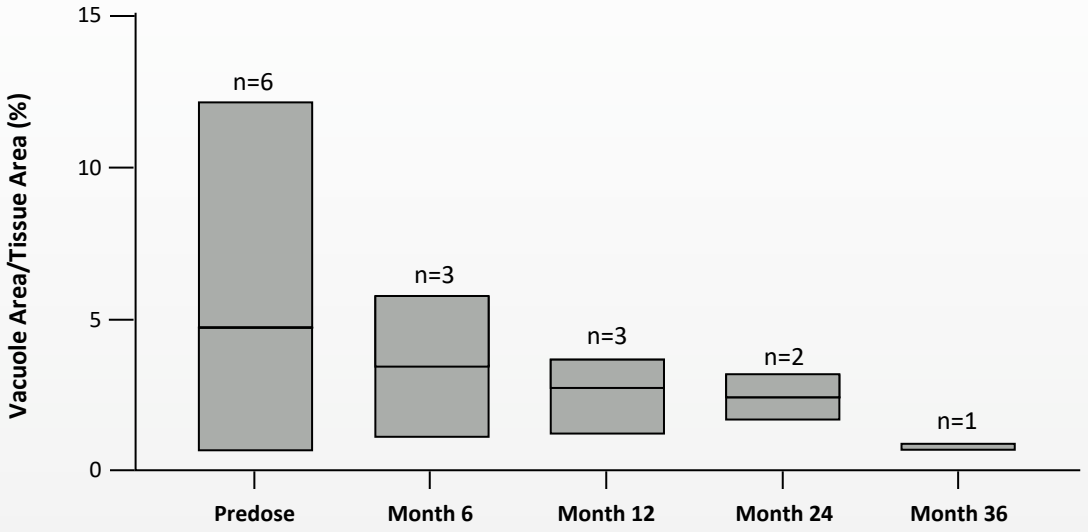


Light microscopy images at 20X;
Autophagic vacuoles are depicted by yellow arrows.

A. Vacuolar Area of Endomyocardial Tissue



B. Vacuolar Area Decreases with Treatment

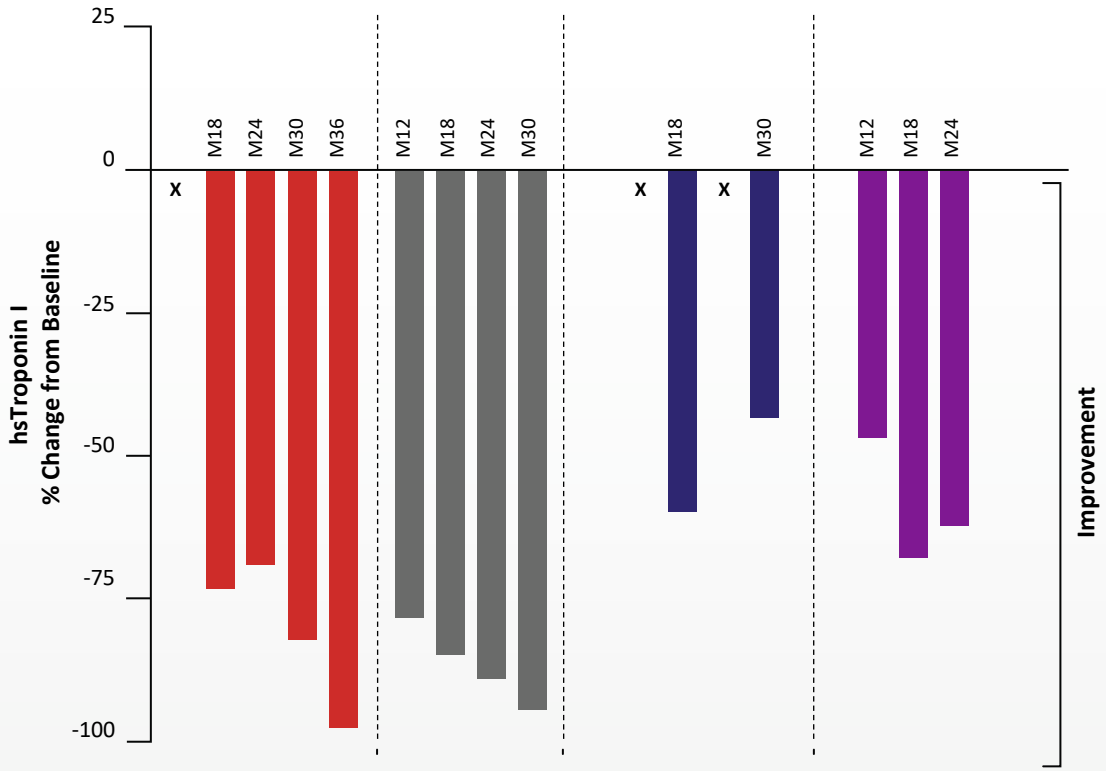


M, month; X, data not assessed

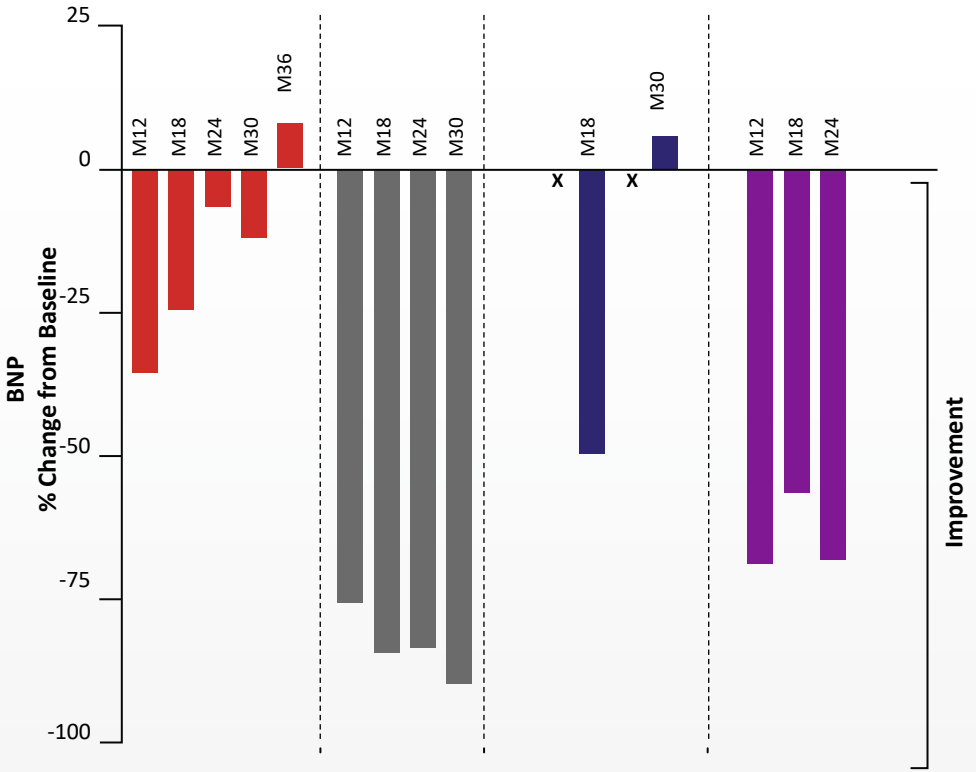
Bars denote minimum and maximum range, and line within each bar represents the mean value within study population.

Sustained Improvement or Stabilization of Biomarkers of Myocardial Injury and Stress Following RP-A501

High Sensitivity Troponin I (hsTnI)



Brain Natriuretic Peptide (BNP)

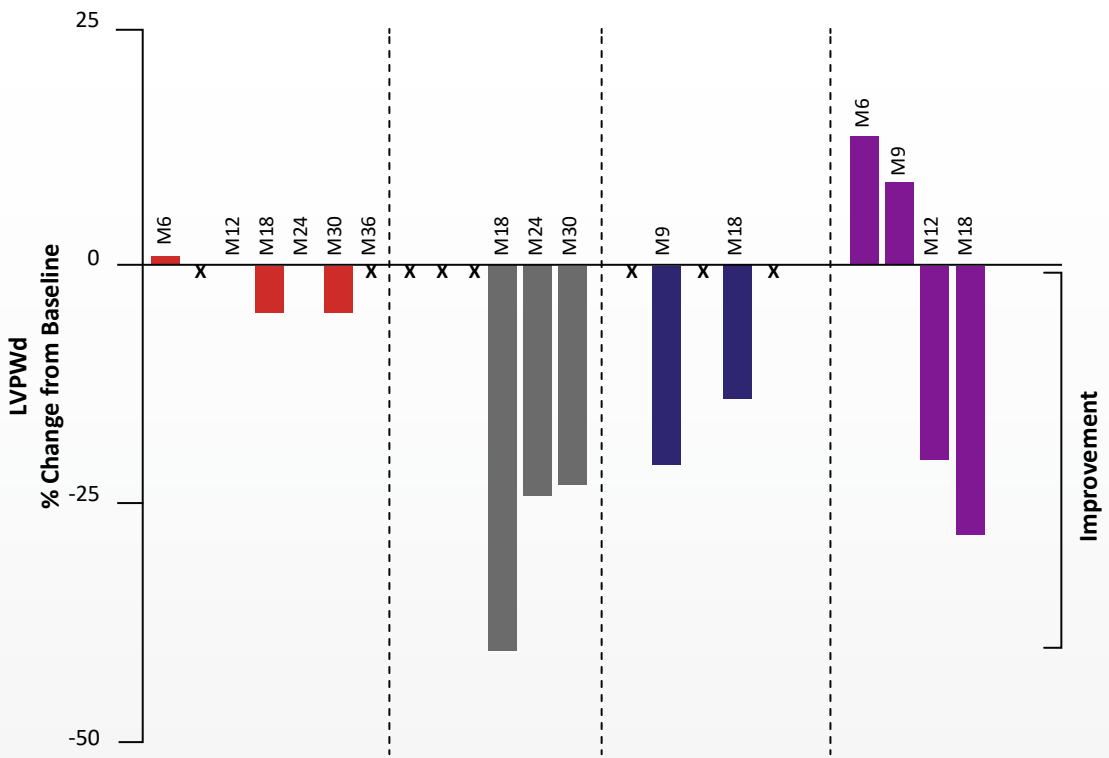


1001 1002 1005 1006

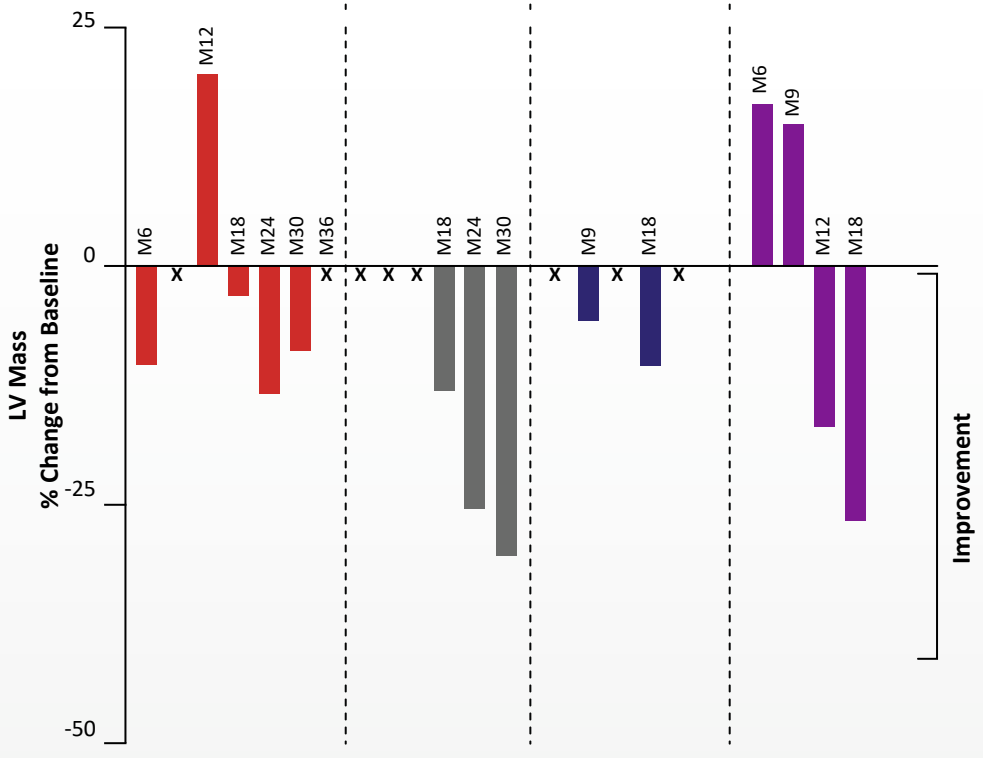
M, month; X, data not assessed

Sustained Improvement or Stabilization of LV Hypertrophy Following RP-A501

LV Posterior Wall Thickness



LV Mass



1001 1002 1005 1006

LV, left ventricle; LVPWd, LV posterior wall end diastole; M, month; X, data not assessed
LV hypertrophy is assessed via LV posterior wall at end diastole (LVPWd) and LV mass.

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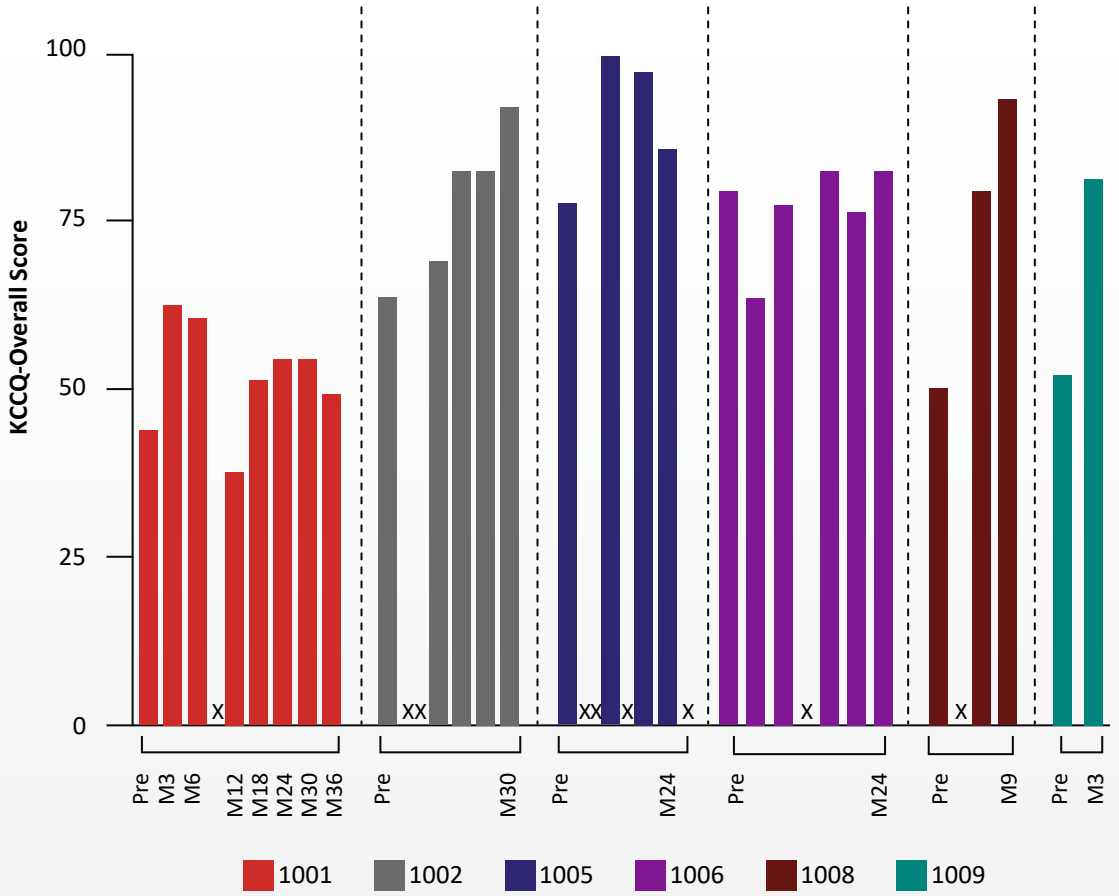
Sustained Improvement or Stabilization of Functional Cardiac Status Following RP-A501

New York Heart Association Class

Cohort	Patient ID	Baseline	Month 12	Most Recent Follow-up	Time of Most Recent Follow-up
Low Dose Adult	1001[a]	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

Kansas City Cardiomyopathy Questionnaire Overall Score



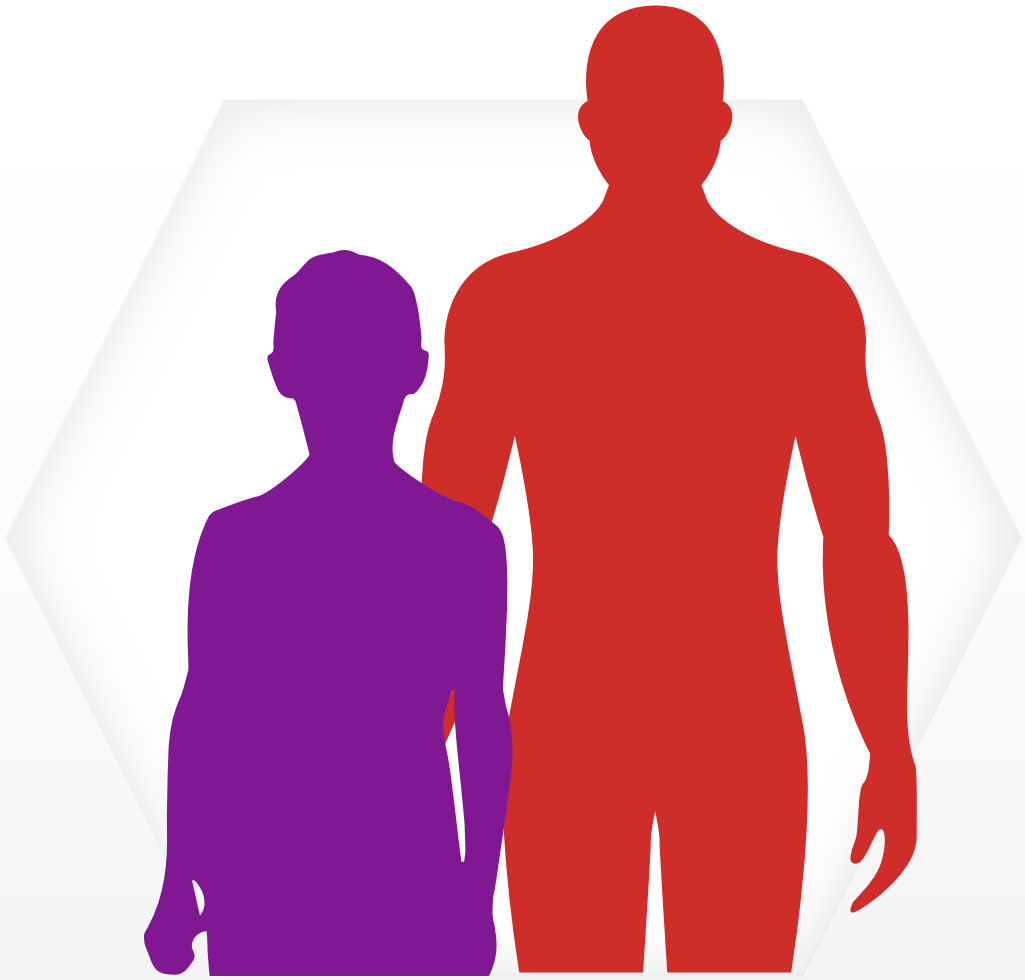
M, month; X, data not assessed.
[a] Corticosteroid compliance uncertain

Conclusion and Next Steps

Summary of Results and Conclusions

PEDIATRIC COHORT

- RP-A501 was well tolerated
- No immediate, early or delayed RP-A501 related SAEs observed to date with enhanced immunomodulation
  - Minimal complement activation
  - Platelets remained within normal range
- Absent or limited worsening of skeletal myopathy with reduced steroid dose and more rapid taper, and introduction of sirolimus
- Increased LAMP2B protein expression was associated with early signals of improved cardiac histology, as well as serological evidence of decreased myocardial injury and stress
- Early improvement in NYHA class and KCCQ for both patients



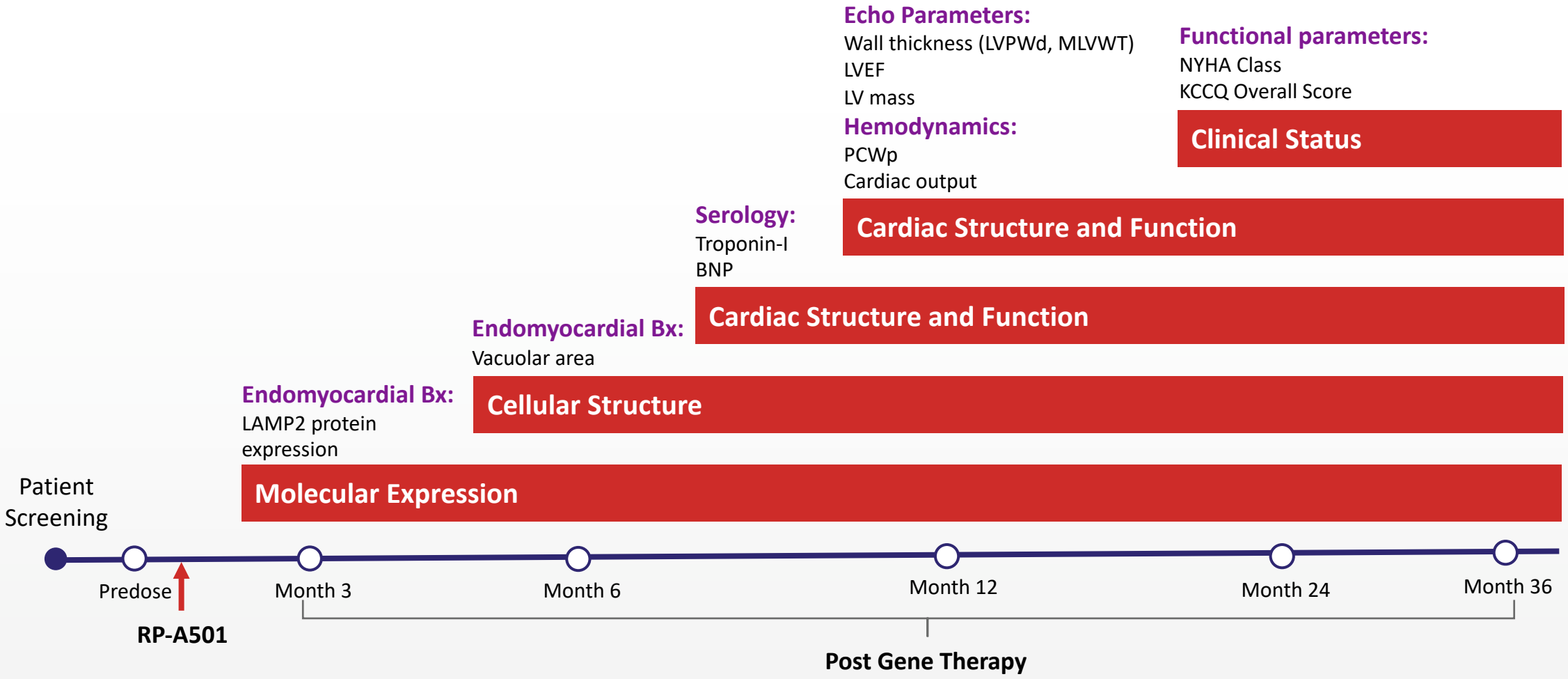
ADULT COHORT

- Low-dose continues to be generally well tolerated at 2-3 years post-treatment
- Increased LAMP2B protein expression was associated with durable disease improvement or stabilization including clinical status (NYHA class, KCCQ), LV hypertrophy (LV wall thickness and mass), biomarkers of myocardial injury and stress (hsTroponin I and BNP), and cardiac histology
- All patients are alive and well in their early 20s, whereas median survival in DD males is 19 years old*

BNP, brain natriuretic peptide; hs, high sensitivity; KCCQ, Kansas City cardiomyopathy questionnaire; LAMP2B, lysosome-associated membrane protein 2B; LV, left ventricle; NYHA, New York Heart Association; SAE, serious adverse event.

*Except for patient 1007 who received a heart transplant at 5 months due to Danon Disease progression. He is currently stable. Brambatti M et al. *Int J Cardiol.* 2019;286:92-98.

Connecting Surrogate Endpoints to Functional Outcomes for Pivotal Study*



BNP, brain natriuretic peptide; Bx, biopsy; KCCQ, Kansas City cardiomyopathy questionnaire; LAMP2, lysosome-associated membrane protein 2; LV, left ventricle; LVEF, LV ejection fraction; LVPWd, LV posterior wall end diastole; MLVWT, maximal LV wall thickness; NYHA, New York Heart Association; PCWp, pulmonary capillary wedge pressure.
*Pending regulatory feedback

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RP-A501-0219 Patient Anecdotes

Patient	Anecdote
1005	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. Another amazing thing we have seen is about 4 months after his therapy trial he started working and stopped using his motorized scooter all together.
1006	We see him smile more now, he makes plans for moving to his own place and working a couple of days a week, he has started to open up for meeting more friends in real life and has gotten a whole new peace of mind now ...he feels better, and he didn't think that would ever happen.
1008	He went to summer camp on his own for the first time and is no longer out of breath walking up stairs.
1009	He walked a 10K with his father following treatment. He is exercise training twice a week for an hour.

Anecdotes, shared by sites or family members, available on four of the six patients whose efficacy data is presented.

Summary of Results and Conclusions

Phase 1 enrollment and treatment are **complete**

- ✓ The enhanced immunomodulatory regimen **was well tolerated and has effectively mitigated adverse events** in the pediatric cohort, who are currently 6 to 11 months post treatment
- ✓ The **early LAMP2 expression data from the pediatric cohort are encouraging and consistent** with that seen in the adult patients at the same timepoints
- ✓ The **early clinical trends for the pediatric cohort are encouraging and consistent** with the **sustained clinical responses seen in the adults at 24-36 months**
- ✓ **Study design and endpoints have been identified** for the planned Phase 2 pivotal study* and **endorsed by an International Scientific and Clinical Advisory Board**; FDA discussion planned at the end of this year

*Pending regulatory feedback