Danon Disease: RP-A501 Phase 1 Results

The First Single-Dose Intravenous (IV) Gene Therapy with Recombinant Adeno-Associated Virus (AAV9:LAMP2B) for a Monogenic Cardiomyopathy

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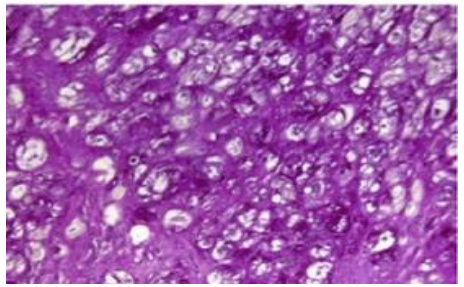
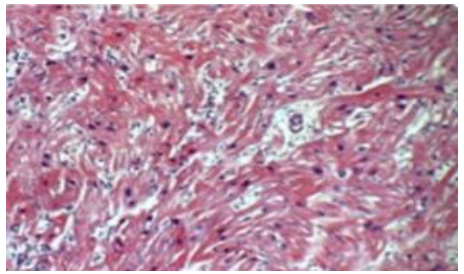
Disclosures

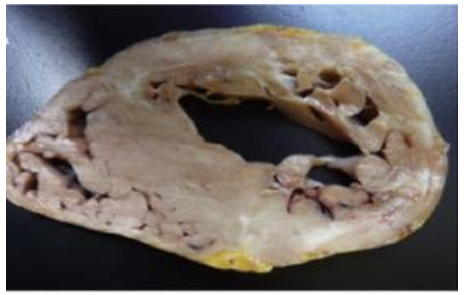
- Consultant: Bristol Myers Squibb, Bayer, Merck, CRI Biotech, American Regent
- Rocket Pharmaceuticals, Inc. is the sponsor of the clinical trial

Danon Disease

Highly aggressive genetic cardiomyopathy due to impaired autophagy







Autosomal dominant, monogenic X-linked disease

- Gene mutation: *LAMP2* (**L**ysosomal **A**ssociated **M**embrane **P**rotein **2**)
- Impaired autophagy
- Prominent sarcoplasmic vacuoles
- Myocardial disarray

Severe Cardiomyopathy (CM)

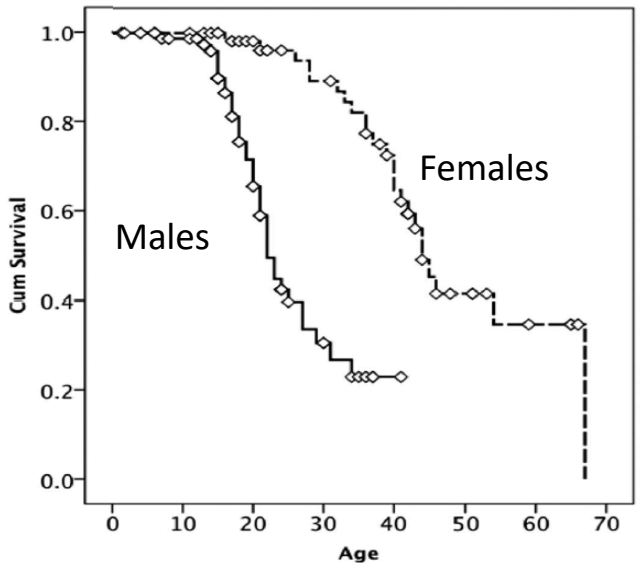
- Mortality secondary to heart failure or arrhythmia
- **Males**:
  - Hypertrophic CM (HCM) with arrhythmias
  - HCM at presentation in >95% of patients
  - Mortality in 2nd to 3rd decades
- **Females:**
  - Dilated/hypertrophic CM and arrhythmias
  - Mortality in 4th to 5th decades

Other Clinical Features

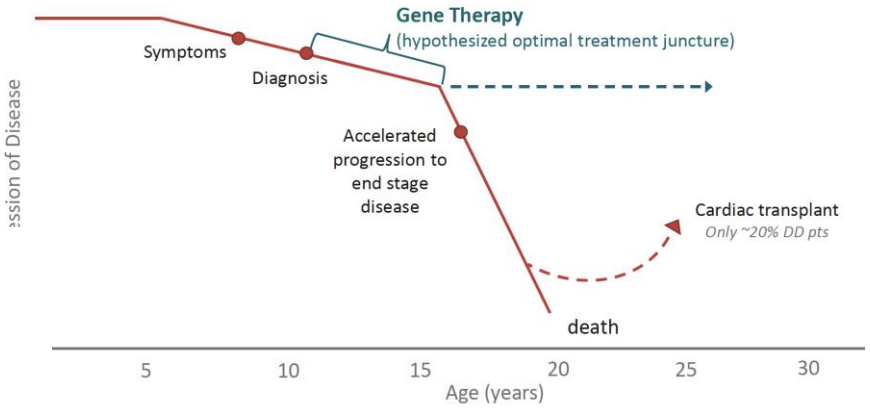
- Skeletal Myopathy, CNS, Ophthalmic manifestations

Rapid decline in second decade of life
Guideline directed HF therapies don't alter disease course/prognosis
Currently, heart transplant is the only definitive intervention

Limited Overall Survival



Males: Critical interval in childhood/ early adolescence precedes rapid decline



Brambatti M et al. Int J Cardiol. 2019;286:92-98; Boucek D, Jirikowic J, Taylor M. Genet Med 2011; 13(6):563-68

RP-A501 (AAV9.LAMP2B): Mechanism of Action and Vector Construct

Goal

- Restore LAMP2B protein expression
- Repair autophagy
- Normalize myocardial structure & function

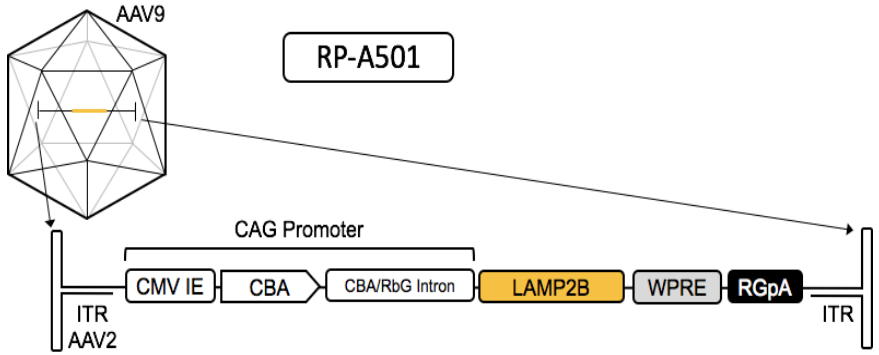
Intravenous Administration of rAAV

- rAAV9 DNA encodes full-length LAMP2B protein
- AAV9: demonstrated myocardial tropism
- Non-dividing, terminally differentiated cardiomyocytes are transduced

Potential toxicities of systemic AAV9

- Acute complement-mediated thrombotic microangiopathy (TMA)[1]
- Hepatotoxicity due to AAV liver accumulation and cell-mediated immunity
- Myocarditis
- Steroid-related skeletal myopathy

AAV9.LAMP2B Construct



[1]Kishimoto TK et al. *Expert Opin Biol Ther.* 2022; 22(9): 1067-71; Ertl HCJ. *Front Immunol.* 2022; 13:975803.

Study Design: Phase 1 Non-Randomized Open-Label Study

Inclusion Criteria

- Male
- Confirmed *LAMP2* mutation
- Cardiac involvement confirmed by imaging or ECG
- NYHA Class II or III

Exclusion Criteria

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

Single I.V. Dose of RP-A501 (AAV9.LAMP2B)

Adults & Adolescents

≥15 years
n=5

Low Dose:
6.7×10^{13} GC/kg

High Dose*:
1.1×10^{14} GC/kg

* No further enrollment at this dose (n=2).

Pediatric

8-14 years
n=2

Low Dose:
6.7×10^{13} GC/kg

36 Month Follow-up

Enrollment Complete

PRIMARY OUTCOMES

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

Baseline Characteristics

Patients had marked left ventricular hypertrophy with elevated BNP and troponins at baseline

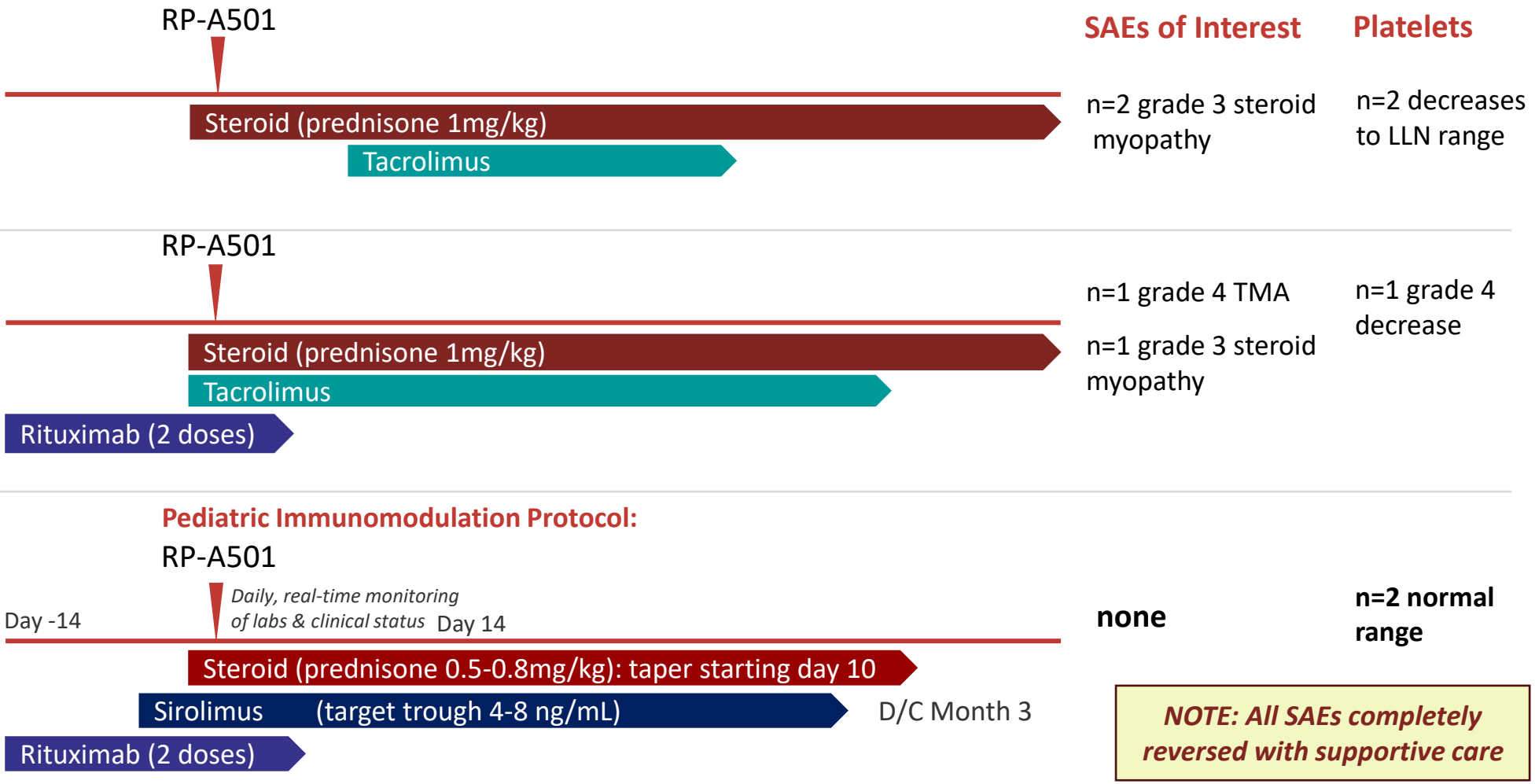
Cohort	Patient ID	Age at RP-A501 Infusion (y)	NYHA Class	LVEF (%)	Max LVWT (mm)	LV mass (g)	BNP (pg/mL)	hsTnI (ng/mL)	KCCQ-12
1: Low Dose Adult/ Adolescent	1001	17.4	II	57	25	311	55	0.6	44
	1002	20.3	II	55	64	989	1308	1.46	64
	1005	18.3	II	65	33	438	166	0.28	77
2: High Dose Adult/ Adolescent	1006	21.1	II	62	22	410	135	0.54	79
	1007	20.7	II	32	27	966	651	2.59	67
1A: Low Dose Pediatric	1008	12.3	II	74	42	605	1837	1.89	50
	1009	11.7	II	77	19	234	297	0.67	52

NYHA: New York Heart Association; LVEF: Left Ventricular Ejection Fraction; LVWT: Left ventricular wall thickness; BNP: brain natriuretic peptide; hsTnI: high sensitivity Troponin-I; KCCQ: Kansas City Cardiomyopathy Questionnaire; Data cut-off July 11, 2022

Low Dose: 6.7 x 10^{13} GC/kg
High Dose: 1.1 x 10^{14} GC/kg

Immunomodulation and Safety

After immunomodulation was optimized, there were no observed TMA or steroid myopathy SAEs

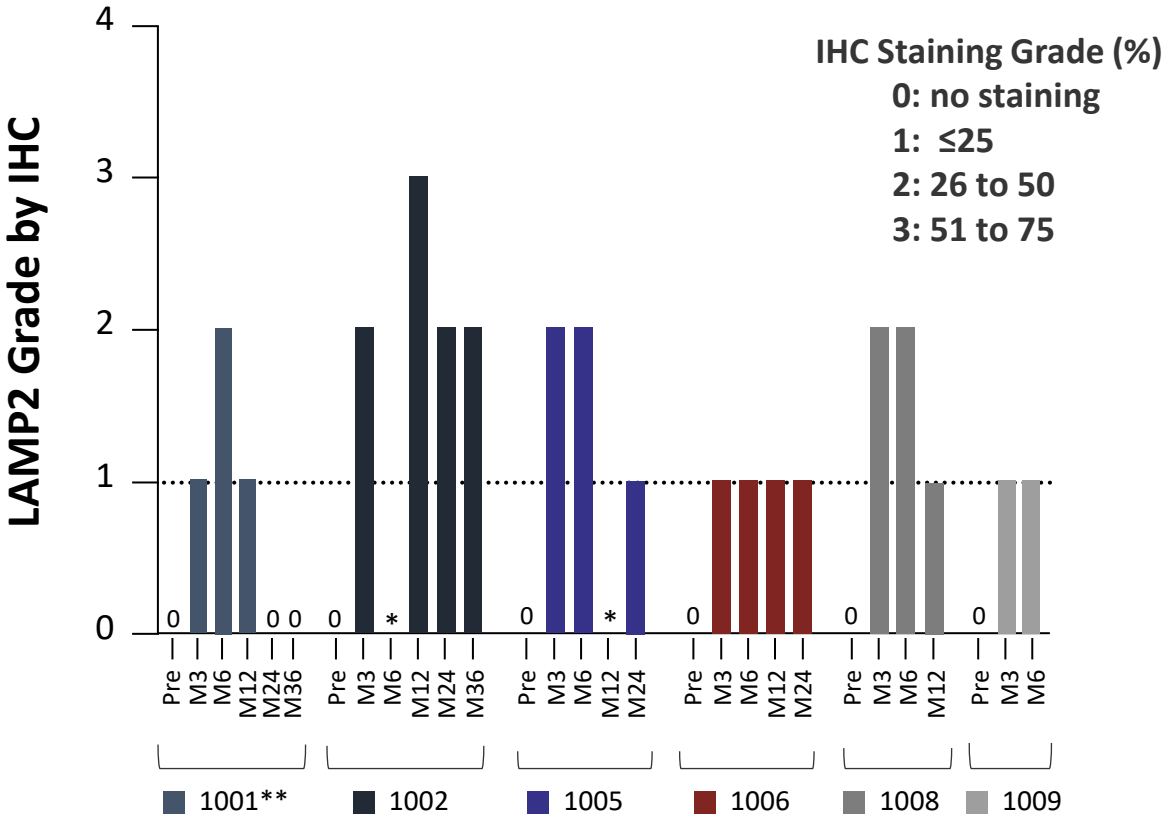


SAE: serious adverse event; LLN: lower limit of normal; TMA: thrombotic microangiopathy; D/C: discontinue; Data cut-off July 11, 2022

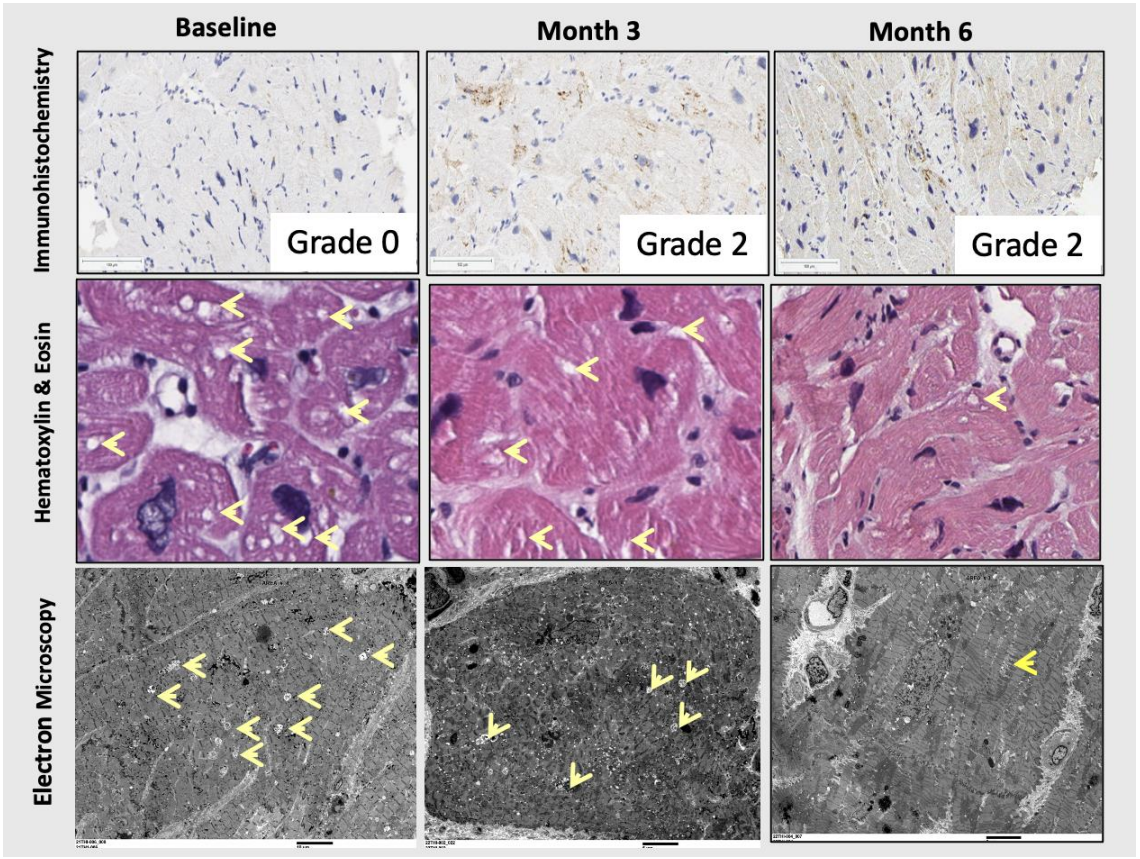
Preliminary Efficacy

Durable Myocardial LAMP2 Protein Expression; Decrease in Size and Number of Vacuoles

Myocardial LAMP2 Protein Expression



Endomyocardial Biopsy Images (A501-008-1008)



LAMP2 protein expression relative to normal controls; entire tissue sample assessed by core lab in a blinded fashion. Percentages reflect estimated extent of LAMP2 staining;
*No data available ** Corticosteroid compliance uncertain. Data cut-off July 11, 2022

LAMP2, lysosome associated membrane protein 2; M, month. IHC = immunohistochemistry;

Improvement or Stabilization from Baseline Observed Across Key Cardiac Biomarker, Echo Findings and Functional Measures

Cohort	Patient ID	Duration of Follow-up (months)	hsTnI (ng/mL)	BNP (pg/mL)	LV mass (g)	Max LV Wall Thickness (mm)	NYHA class	KCCQ score
Low dose adult/ adolescent	1001	36	0.6 ⇢ 0.01	55 ⇢ 59	311 ⇢ 212	25 ⇢ 23	II ⇢ II	44 ⇢ 49
	1002	36	1.46 ⇢ 0.06	1308 ⇢ 80	989 ⇢ 511	64 ⇢ 38	II ⇢ I (M30)	64 ⇢ 81
	1005	30	0.28 ⇢ 0.15	166 ⇢ 176	438 ⇢ 375	33 ⇢ 24	II ⇢ I	77 ⇢ 85 (M24)
High dose adult/ adolescent	1006	24	0.54 ⇢ 0.20	135 ⇢ 42	410 ⇢ 300	22 ⇢ 18	II ⇢ I	79 ⇢ 82
Low dose pediatric	1008	12	1.89 ⇢ 0.26	1837 ⇢ 306	605 ⇢ 432 (M9)	42 ⇢ 36 (M9)	II ⇢ I	50 ⇢ 82
	1009	6	0.67 ⇢ 0.07	297 ⇢ 113	234 ⇢ 185	20 ⇢ 20	II ⇢ I	52 ⇢ 78

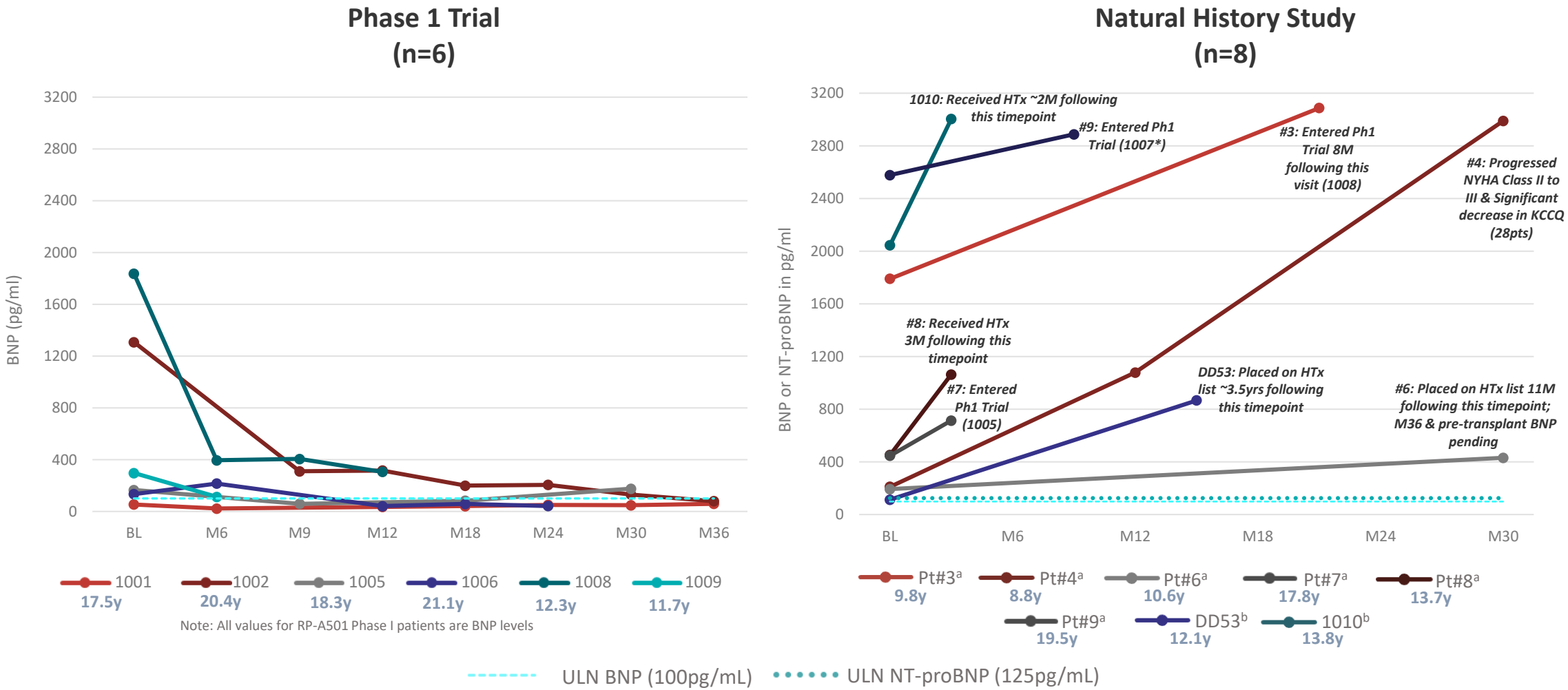
- No patients worsened from BL to most recent visit on any of these parameters
- All showed improvements for many of these parameters
- Those who did not show improvement demonstrated no appreciable change i.e. stabilized

Improved Stabilized Worsened

BNP, brain natriuretic peptide; DD, Danon disease; hsTnI, high-sensitivity troponin I; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAMP2, lysosome-associated membrane protein 2; LV, left ventricle; NYHA, New York Heart Association.
Does not include pt 1007 in Ph1 trial who had advanced HF with EF<40% at enrollment and received HTx 5M following tx due to pre-existing advanced HF. Patient is currently stable. Data cut-off July 11, 2022

Phase 1 Trial vs. Natural History Study: Contrast in Disease Progression as Measured by Natriuretic Peptides

Natriuretic peptides improved or stabilized in Phase 1 compared to progressive increases in the NHS



[a]NT-proBNP tends to be higher than corresponding [b]BNP values given longer plasma half-life. NHS: patients from prospective NHS (patients 3,4,6,7,8,9), natural history (DD53) and screen failure from Phase I study (1010). Phase I graph: BNP levels only: does not include pt 1007 who had advanced Hf (EF<40%) at enrollment and received HTx 5 months following RP-A501 treatment due to pre-existing advanced HF. Patient is currently stable.

Summary and Conclusion:

Phase 1 Demonstrated a Favorable Benefit-Risk Profile for RP-A501 in Pediatric, Adolescent and Adult Males

- RP-A501 was associated with favorable safety at the low dose ($6.7x10^{13}$ GC/kg) with an appropriate immunomodulatory regimen
- All patients that remain in follow-up demonstrated improvement or stabilization across key clinical, biomarker, echocardiographic, and QoL parameters, indicating preliminary evidence of efficacy
- Improvement or stabilization of disease progression in patients treated with RP-A501, as measured by natriuretic peptides, was in direct contrast to progressive worsening observed in patients in the NHS
- As of May 2023, all patients that remain in follow-up continue to show signs of improvement or stabilization; additional follow-up data to be provided at a future date
- All data to date support positive risk-benefit profile of RP-A501 and advancement to a pivotal global Phase 2 study; anticipated start in 2Q 2023

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