Rocket Pharmaceuticals
Danon Disease Program Update

September 11, 2023

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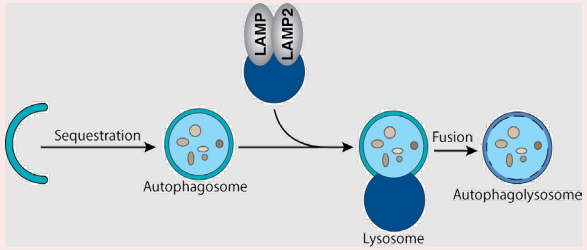
SEEKING GENE THERAPY CURES

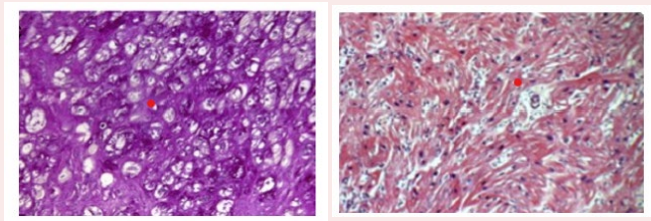
Danon Disease

Aggressive genetic hypertrophic cardiomyopathy with very high early mortality

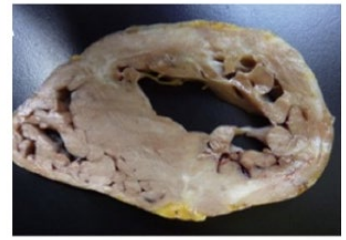
1 Gene mutation leads to decreased LAMP2B protein and impaired autophagy



2 Impaired autophagy leads to ↑ vacuoles, myocyte hypertrophy, necrosis, & fibrosis

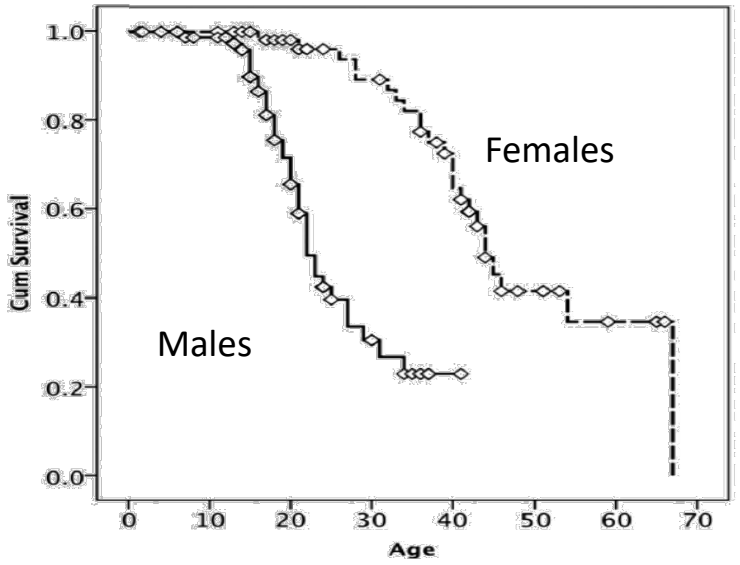


3 Pathologic processes lead to phenotype of extreme LV hypertrophy and cardiomyopathy



- **Danon Disease is the most aggressive and lethal hypertrophic cardiomyopathy**
- **Monogenic, X-linked disease progresses to severe cardiomyopathy at early ages; characterized by massive LV hypertrophy and end-stage heart failure**
- **Uniformly fatal with early mortality (*males ~19 yrs.; females ~37 yrs.)***
- **Only definitive treatment is cardiac transplantation, availability is limited, and associated with extensive short- and long-term morbidity and mortality (<50% 10-yr survival post HTx)**

4 Natural History: High rates of death at early ages



Cenacchi G et al. Neuropathol. Appl. Neurobiol. 2020; Rowland T et al. J Cell Sci. 2016; Boucek D, Jirikowic J, Taylor M. Genet Med 2011; Thrush P et al. J Thorac Dis. 2014; Dipchand A et al. J Heart Lung Transplant. 2014

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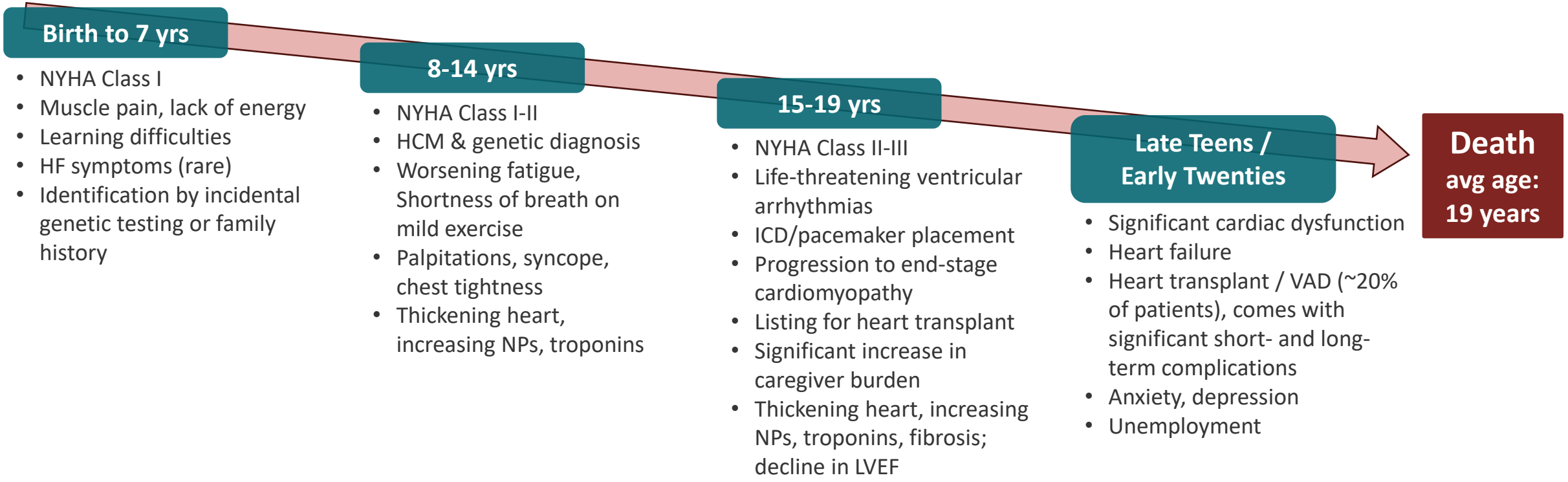
Natural History: Progression of Danon Disease in Male Patients

Critical interval in childhood / early adolescence precedes rapid decline, providing optimal window of opportunity for GTx
Patients typically on maximal medical management (e.g. beta blockers, ICD) - none alter disease progression



Note: Danon disease is a life-threatening and seriously debilitating condition. Above are not meant to be a strict categorization of symptoms/outcomes by age. Heart failure and death from Danon disease can occur well before the patient reaches his twenties. **Of note, the four adult patients in the Phase 1 study with 2.5-3.5 yr follow-up post gene therapy are currently alive, clinically stable, and free from Danon disease progression at ages 21-24 years old – in contrast to the trend in the natural history of this disease.**

NYHA = New York Heart Association Class; ICD: implantable cardioverter-defibrillator; HTx = Heart Transplantation; VAD: Ventricular Assist Device

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

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Phase 1 Data: Benefit Observed Across All Key Clinical Parameters

Early LAMP2, BNP, TnI changes associated with sustained clinical improvement and guided Phase 2 endpoint selection

Cohort	Patient ID	Follow-up (months)	**Myocardial LAMP2 Grade (≤M12)**	TnI Δ (≤M12)	BNP Δ (≤M12)	**LV mass Δ (g)**	**LV Mass Index Δ (g/m^2.7)**	Max LV Wall Thickness Δ (mm)	NYHA class Δ	KCCQ score Δ
Low dose adult/ adolescent	1001	36	1	-75% (M18)	-36%	311 ⇢ 212	85 ⇢ 57	25 ⇢ 23	II ⇢ II	44 ⇢ 49
	1002	36	3	-79%	-76%	989 ⇢ 511	260 ⇢ 129	64 ⇢ 38	II ⇢ II	64 ⇢ 81
	1005	30	2 (M9)	-57% (M9)	-64% (M9)	438 ⇢ 375	98 ⇢ 76	33 ⇢ 24	II ⇢ I	77 ⇢ 85 (M24)
High dose adult/ adolescent	1006	24	1	-47%	-70%	410 ⇢ 300	90 ⇢ 63	22 ⇢ 18	II ⇢ I	79 ⇢ 82
Low dose pediatric	1008	12	1	-86%	-83%	605 ⇢ 447	140 ⇢ 96	42 ⇢ 39	II ⇢ I	50 ⇢ 82
	1009	6	1	-90%	-62%	234 ⇢ 185	83 ⇢ 63	20 ⇢ 20	II ⇢ I	52 ⇢ 78

All specified parameters either improved or stabilized (none deteriorated)

Improved Stabilized Worsened

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. BNP, brain natriuretic peptide; hsTnI, high-sensitivity troponin I; KCCQ, Kansas City Cardiomyopathy Questionnaire; LAMP2, lysosome-associated membrane protein 2; LV, left ventricle; NYHA, New York Heart Association. Data cut-off Oct 6, 2022; Grade 0=negative staining; Grade 1 ≤25%; Grade 2 =26%-50%; Grade 3 =51%-75%; Grade 4 >75%. Low dose = 6.7×10^{13} GC/kg, high dose = 1.1×10^{14} GC/kg

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Latest Pediatric Data Shows Sustained Improvements in Biomarkers, Symptoms, and Function (Updated Data)

Subject ID: A501-008-1008

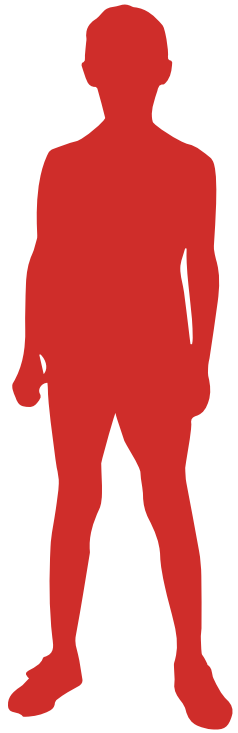
Baseline Characteristics

AGE AT INFUSION
12.3 years
ICD yes[1]
WPW yes

MAX LV WALL THICKNESS
41.9 mm, z-score +32
6MWT
438 meters

18 months

Variable	Baseline[2]	Most Recent Follow-up
LAMP2 protein[3]	0	1 (M12)
Troponin-I (ng/mL)	1.89	0.30 (-84%)
BNP (pg/mL)	1837	328 (-82%)
NYHA Class	II	I
LV Mass Index	140	96 (-31%)[4]



Subject ID: A501-008-1009

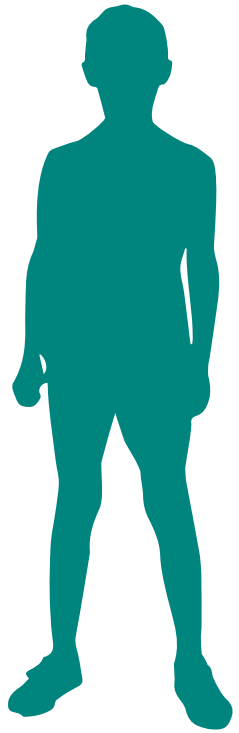
Baseline Characteristics

AGE AT INFUSION
11.7 years
ICD no
WPW no

MAX LV WALL THICKNESS
19.8 mm, z-score +12
6MWT
553 meters

12 months

Variable	Baseline[2]	Most Recent Follow-up
LAMP2 protein[3]	0	1 (M6)
Troponin-I (ng/mL)	0.67	0.08 (-88%)
BNP (pg/mL)	297	163 (-45%)
NYHA Class	II	I
LV Mass Index	83	60 (-28%)[4]



[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] Extent of LAMP2 expression grading: Grade 0 = negative staining, Grade 1 < 25%, Grade 2 = 26-50%, Grade 3 = 51-75%, Grade 4 > 75%. [4]M12 Note: All data preliminary, not yet validated.
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.

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FDA Engagement and Alignment on Danon Program

Since the EOP1 Meeting in November 2022, Rocket has had collaborative formal and informal discussions with FDA to align on the optimal pivotal Phase 2 study design

Previously Disclosed Trial Elements

- ✓ *Pivotal, single-arm study*
- ✓ *Peds safety run-in*
- ✓ *Dosage ($6.7x10^{13}$ GC/kg)*
- ✓ *Safety protocol & management plan*
- ✓ *CMC (product comparability and potency assay)*
- ✓ *NHS to serve as external comparator*
- ✓ *RMAT designation granted*

Recent Engagement and Alignment

- ✓ *F2F meeting with review team and senior FDA leadership*
- ✓ *Co-primary endpoint to support accelerated approval consisting of LAMP2 expression & LV Mass reduction of ≥ 10%*
- ✓ *N=12 patients for pivotal study with potential for primary endpoint readout at 12 months*
- ✓ *Study to support AA with a path towards conversion to full approval (with longer follow-up)*

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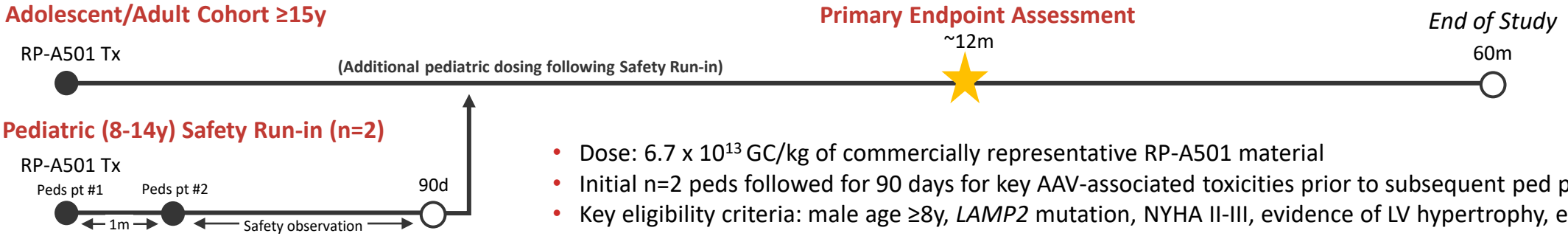
Phase 2 Trial Design – 12 Patients with 12-month Primary Endpoint Duration

Pivotal, global, single-arm, open label study with external comparator

PIVOTAL PHASE 2 STUDY DESIGN



- Dose: 6.7 x 10^{13} GC/kg of commercially representative RP-A501 material
- Initial n=2 peds followed for 90 days for key AAV-associated toxicities prior to subsequent ped pt enrollment
- Key eligibility criteria: male age ≥8y, *LAMP2* mutation, NYHA II-III, evidence of LV hypertrophy, elevated hsTnI

CO-PRIMARY ENDPOINT (AA)

- LAMP2 protein ≥ Grade 1 (IHC) AND
- Left Ventricular Mass (LV Mass): ≥10% ↓

SECONDARY & EXPLORATORY ENDPOINTS

- hs-troponin I (key secondary)
- Natriuretic peptides
- QoL instruments (KCCQ, PedsQL, PGI-C, PGI-S)
- NYHA Class
- 6MWT
- Event free survival
- Treatment emergent safety events
- Actigraphy

RISK MANAGEMENT PLAN, TRIAL OVERSIGHT

- Immunomodulatory regimen of Rituximab, Sirolimus, corticosteroids.
- Clinical monitoring team to closely monitor labs, clinical sequelae for AAV-associated toxicities.
- IDSMC: expertise in adult and pediatric cardiomyopathy, immunology, and biostatistics

CONCURRENT NATURAL HISTORY STUDY

Tx, treatment; LV, left ventricular; NYHA; IDSMC, Independent Data Safety and Monitoring Committee; hs-troponin I; KCCQ; HF; m, month; y, year; pts, patients

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Prospective, Retrospective Natural History Study as External Comparator

Allows for robust comparisons and aligned with FDA guidance

Prospective Natural History Study

9 Males + 1 Female

Initiated in 2019, study complete

US Retrospective Natural History

51 Males + 67 Females

Initiated in 2006

EU Retrospective Natural History Study

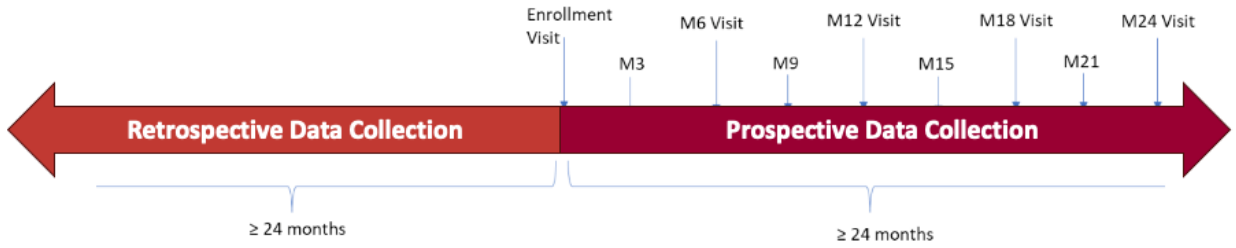
21 Males + 38 Females

Enrollment complete; analysis in Q4 2023

To be expanded through an additional prospective Rocket-initiated natural history study

Key Elements of Study Design:

- Entry criteria and endpoints similar to Phase 2 trial
- Appropriate matching to ensure robust comparisons
- Retrospective data collection to supplement prospective evaluation to ensure sufficient comparative data



HTx, heart transplant; LVEF, LVEF, left ventricle ejection fraction.

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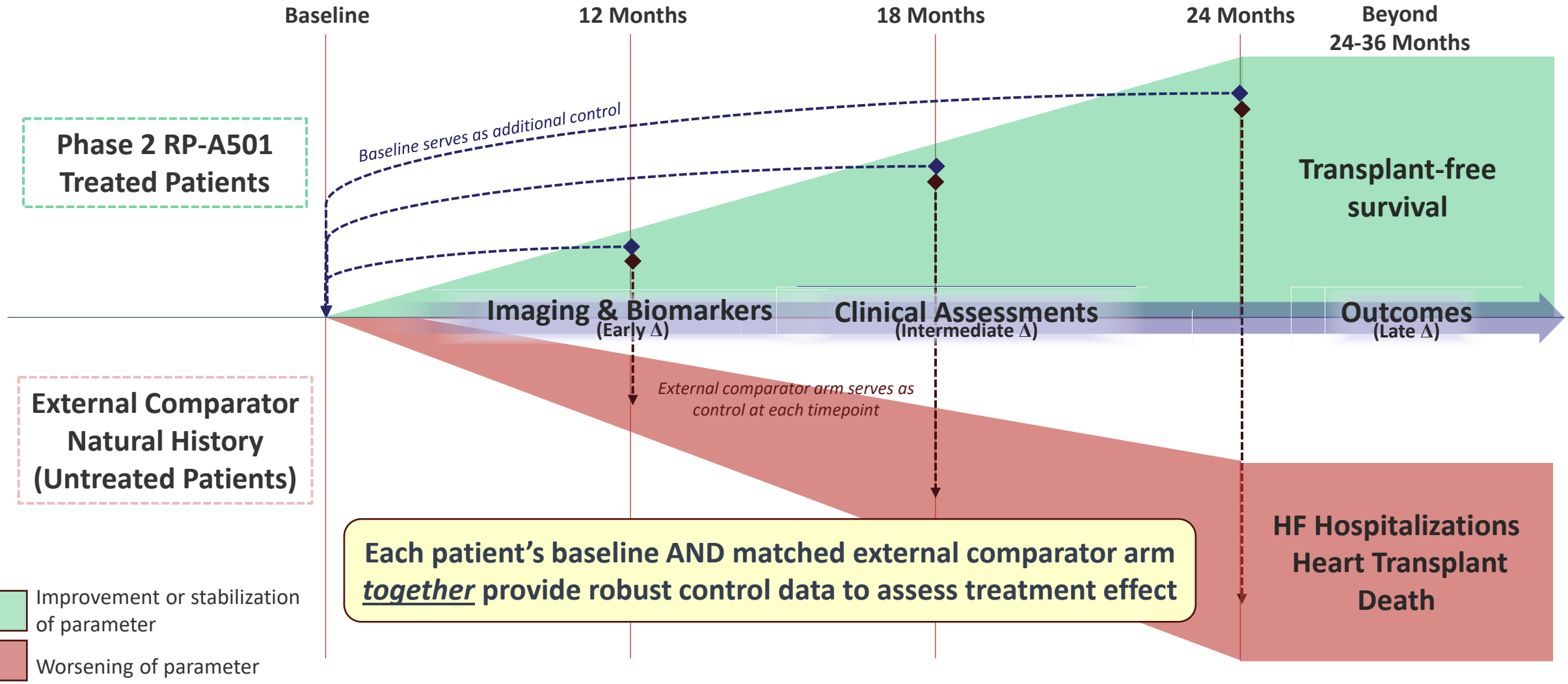
Totality of Evidence to Demonstrate Treatment Effect



Note: Illustrative representation of potential treatment effects versus natural history

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Co-Primary Endpoints for Accelerated Approval

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Primary Endpoint Is Reasonably Likely to Predict Clinical Benefit

Justification for use of LAMP2 protein expression and LV Mass

WT Full Length LAMP2 Protein Expression

- Mutation of *LAMP2* is root cause of Danon disease
- Epidemiologic support: even modest levels of LAMP2 confer a 2-decade survival advantage in female patients
- RP-A501 delivers full coding sequence of WT *LAMP2* gene
- Pre-clinical LAMP2 restoration conferred histologic, functional and survival benefits in LAMP2 knock-out model[1]
- Phase 1: LAMP2 expression associated with decreased vacuolar area, improved myofibrillar disarray, clinical improvement

Left Ventricular Mass

- Largest known hearts are Danon disease hearts
- Severity of the cardiomyopathy in Danon disease is the major prognostic factor[2]
- Retrospective natural history shows year-over-year increases in LV mass in Danon disease patients
- Phase 1: Consistent and significant reductions in LV mass as early as 6 months by echocardiography and cardiac MRI

Primary Endpoint Will Be Interpreted in a Clinical Context:

- *All components are measurable and unlikely to improve in the absence of a true treatment effect*
- *Primary endpoint will be assessed in the context of biomarkers, symptoms, QOL, clinical events derived from secondary endpoints and concurrent natural history study*
- *Phase 1 trial: LAMP2 expression and LV Mass improvements seen as early as 6 months in pediatric subjects with updated immunomodulation regimen*

[1] Manso 2020. *Sci Transl Med.*; [2] D'souza 2017. *J Community Hosp Intern Med Perspect*.

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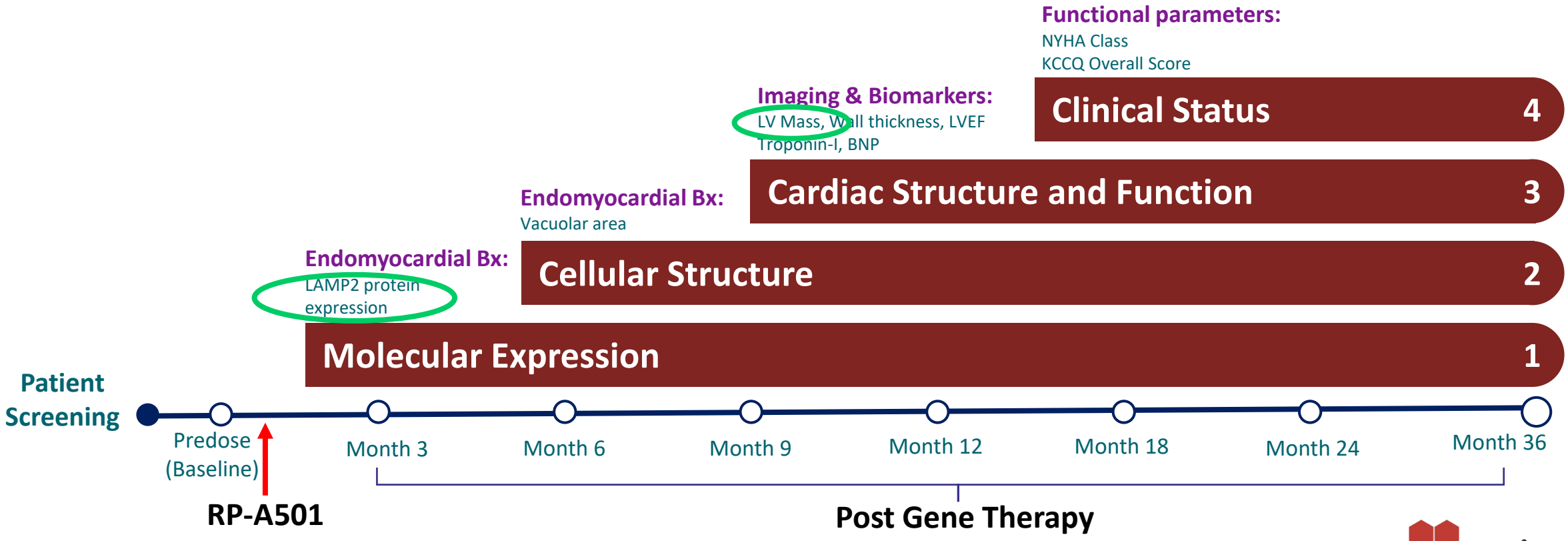
Mechanistic Pathway: Protein Expression to Cardiac Structure to Clinical Outcomes

Improvements Across Cellular, Cardiac Imaging and Functional Measures in Phase 1 Study

LAMP2 expression and LV Mass are mechanistically linked to functional measures and clinical outcomes; reasonably likely to predict clinical benefit



Note: 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

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LAMP2 Protein Expression as Co-Primary Endpoint

*RP-A501 encodes **full-length, wild-type LAMP2B**; cardiomyocytes are **non-dividing cells***

- ***LAMP2* mutation** and associated protein deficit is the **root cause** of Danon disease pathology
- **Grade ≥1 LAMP2** correlates with **evidence of efficacy** in Ph1
  - Absent expression at baseline (Grade 0) in all male patients
  - Improved cardiac biomarkers & hypertrophy, PRO/QOL and NYHA Class – sustained to 3+ years in adult patients, and 12+ months in pediatric patients
  - **Efficacy consistent** in patients with **Grade 1 vs. Grade >1 LAMP2** expression
- Ph1 expression correlates with ↓ autophagic vacuoles and improved myofibrillar disarray, cardiac biomarkers and hypertrophy
- In Danon females, **partial LAMP2 expression** associated with **~2 decade longer survival** than males

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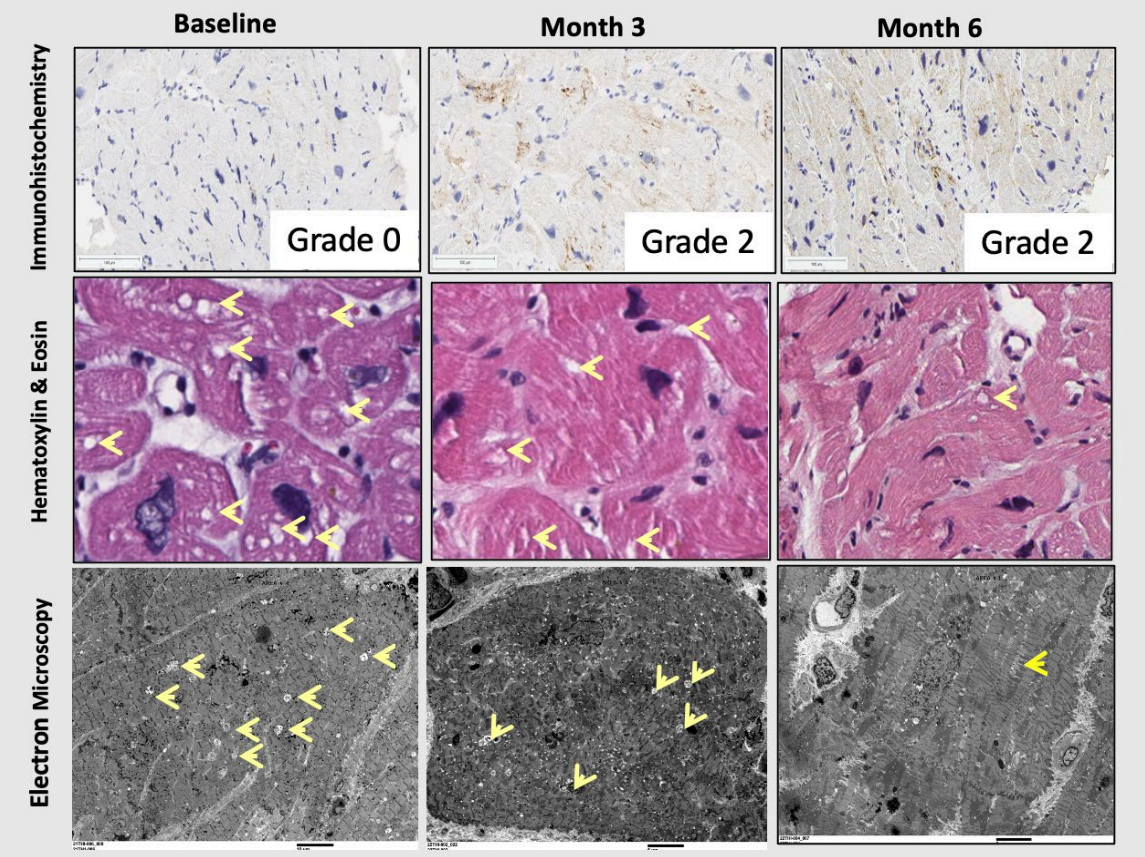
RP-A501 Increases LAMP2 Protein and Decreases Vacuolization

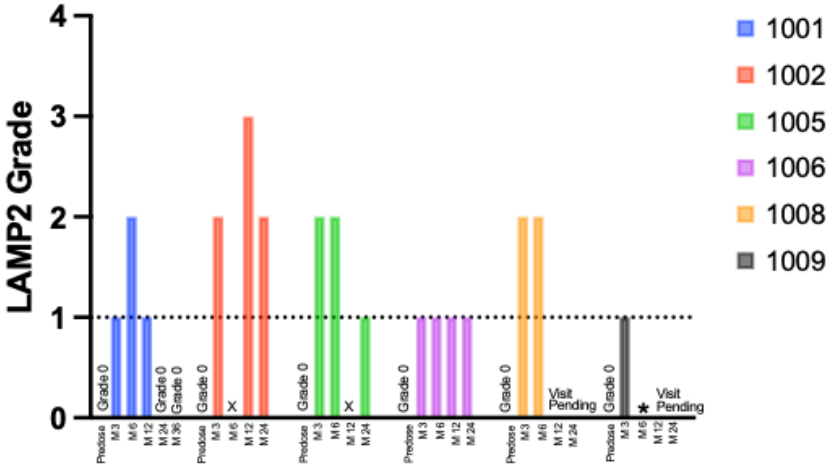
Enhanced autophagy leads to improved myocardial ultrastructure and clinical phenotype

Endomyocardial Biopsy Images

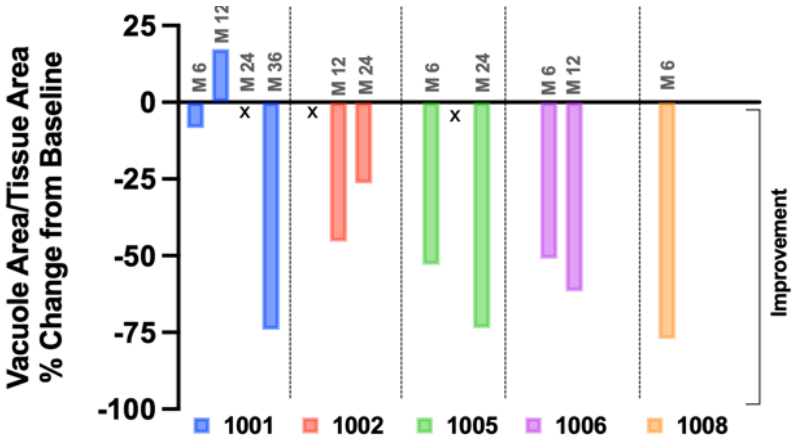
(Subject 1008, RP-A501 Phase 1 Study)



Myocardial LAMP2 Protein Expression



Vacuolar Area of Endomyocardial Tissue



Rocket AHA 2022 Poster Presentation reflects September 27, 2022 data cutoff. LAMP2, lysosome associated membrane protein 2; M, month. IHC = immunohistochemistry

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Left Ventricle Mass as Co-Primary Endpoint

- Danon Disease is **fundamentally a disease of enlarged hearts**; the largest known hearts have been from Danon patients
- Left ventricular hypertrophy is the most consistent phenotypic **feature of disease progression**
- Left ventricular wall thickness has been shown to be a **significant predictor of CV events in cardiomyopathy**
- Meaningful **LV Mass decreases seen as early as 6-9M** in Phase 1 pediatric cohort, and LV Mass Index decreases **sustained to up to 36M in adult patients;** stark contrast to natural history
- In Phase 1 study, LV Mass **significantly correlated with improvements / stabilization in all parameters** including biomarkers (hsTnI, BNP), quality of life (KCCQ), and symptoms (NYHA)

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LVH Predicts Clinical Outcomes in HF and Cardiomyopathies

Cardiomyopathy or CVD	Measure of LVH	Event	HR; CI; p value
HFpEF (Shah 2019)	LV Mass index	CVD or HFH	HR 1.05 per 10 g/m(2); CI 1.00 to 1.10; p = 0.03
HFpEF (de Simone 2008)	LV Mass index	HF	HR 1.03; CI 1.02-1.04; p<0.00001
HCM (Liu 2016)	LV wall thickness	All Cause Death	HR 1.48; CI 1.01 to 2.17; p<0.05
HCM (Liu 2016)	LV wall thickness	CV Death	HR 2.17; CI 1.06 to 1.89; p<0.05
HCM (Liu 2016)	LV wall thickness	Sudden Cardiac Death	HR 3.17; CI 1.64 to 6.13; p<0.05
Fabry Disease (Orsborne 2022)	LV Mass index	Composite of CV events (HFH, MI, procedures, arrhythmias)	HR 1.008; CI 1.003-1.014; p=0.005
Fabry Disease (Hanneman 2020)	LV Mass index	Composite of CV events (HF, ventricular arrhythmia, cardiac death)	HR 1.1 per 5 g/m^2; CI 1.04-1.2; p<0.001

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Shah A, JACC 2019; de Simone G. Eur Heart J. 2008; Liu, Q, Scientific Reports, 2016; Orsborne C, JACC, 2022; Hanneman K. Radiology. 2020

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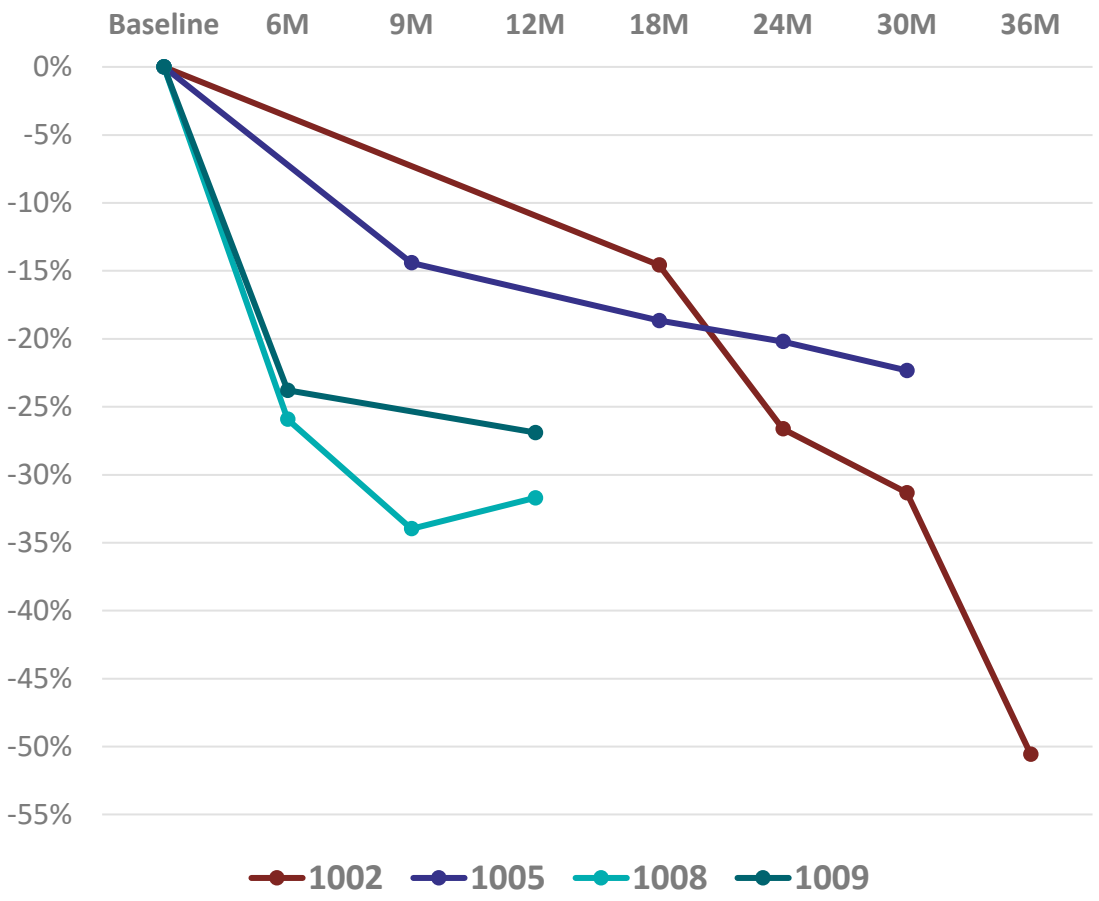
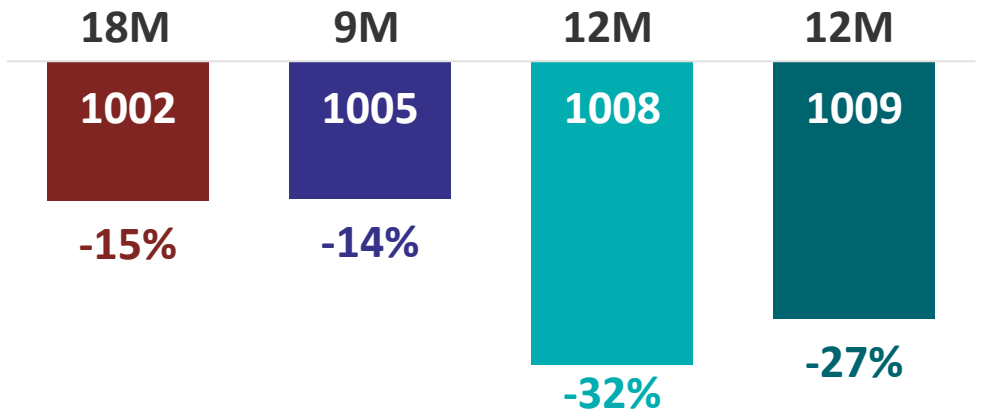
LV Mass Index in RP-A501 Phase 1 Study

RP-A501 Phase 1 Low-Dose Cohort: LV Mass Index % Change from Baseline[1]



RP-A501 Phase 1 Study: LV Mass Index % CFB at ~12M

(9M or 18M where 12M not available)[2]



- **>20% LVMI decrease observed as early as 6M in pediatric cohort, sustained to 12M timepoint**
- **Adult patients with appropriate immunomodulation show >10% LVMI decrease around 12M[2] with further decreases out to 30-36M of 22% to 51%**

[1] Does not include patient 1001 (unmonitored immunomodulation). [2]12M visit data missing for 1002 and 1005 due to pandemic-related travel issues.

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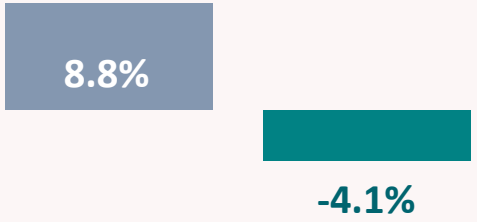
LV Mass / LV Mass Index (LVMI) Improves in DD with RP-A501

LV hypertrophy decreases greater than/comparable to other approved therapies

Fabry Disease

(Agalsidase alfa)

LV Mass @6M



Clinical Correlation:

- *Improvements in LVM out to 36M correlated with HF symptoms (NYHA, CCS); drug approved in EU*

Amyloid Cardiomyopathy

(Patirisan)

LV Mass @18M

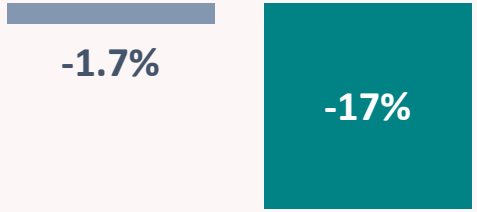
Clinical Correlation:

- *Drug approved based on improved CV outcomes @30M*
- *Significant improvements in 6MWD & NT-proBNP*

HCM

(Mavacamten)

LVMI @7M

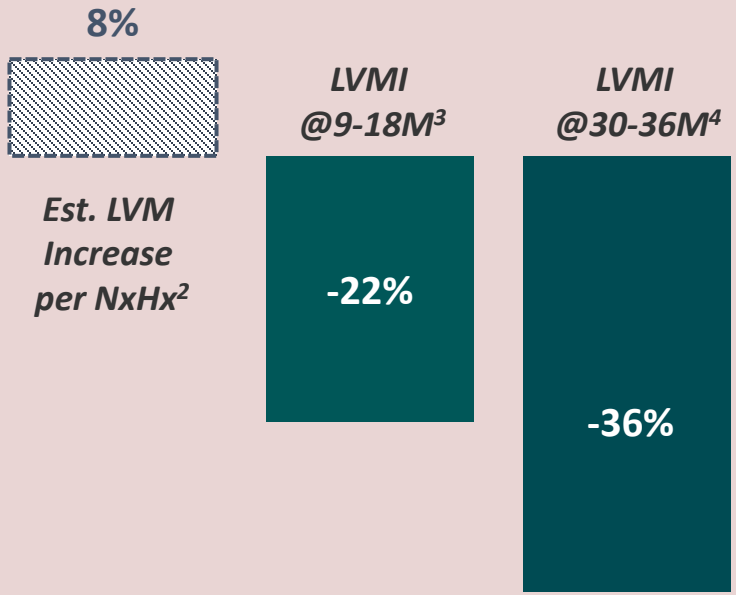


Clinical Correlation:

- *↑ exercise tolerance at 30 weeks*
- *NYHA Class ↓ by 1 in 76% treated patients at 120wks*

Danon Disease[1]

(RP-A501 Low-dose cohort)



Clinical Correlation:

- *NYHA Class improvement, KCCQ ↑, improvement or stabilization in hsTnI and natriuretic peptides all to most recent timepoint (12-36M)*

Placebo / Untreated | **Estimate from retrospective NxHx Data** | **Treated**

[1] RP-A501 Phase 1 low-dose cohort data; averages do not include 1001 (unmonitored immunomodulation) and 1006, 1007 (high dose patients). [2] Reflects estimated LV Mass increase over 12-18M for DD patients based on retrospective natural history data-set (shown on slide 20). [3] Reflects average of 1002 18M, 1005 9M, 1008 12M, 1009 12M. [4] Reflects average of 1005 30M, 1002 36M
Hughes 2008. Heart; Solomon 2019. Circulation; Saberi 2021. Circulation

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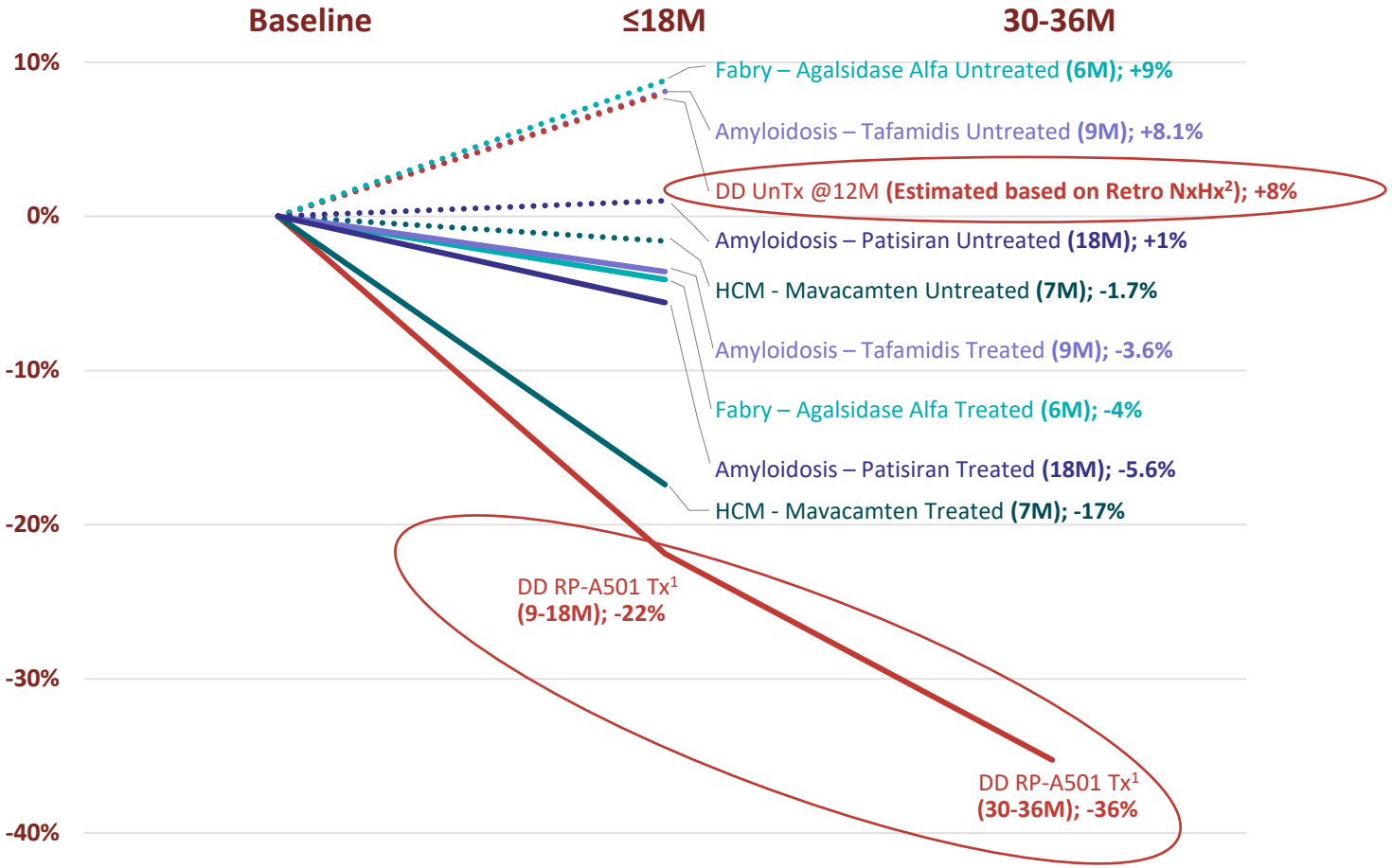
LV Mass in RP-A501 Low-Dose Cohort Versus Recently Approved CV Therapies

LV Mass / LVMI Change from Baseline in Treated vs Untreated Patients: RP-A501 Low-Dose Cohort[1] and Recently Approved CV Therapies



- **Data from Phase 1 study shows RP-A501 is potentially transformative for cardiac structure improvements and remodeling**
- **On par with recently approved therapies in other CV indications (across different disease etiologies and drug MOA's)**

[1] Averages do not include patient 1001 (unmonitored immunomodulation) and 1006, 1007 (high-dose cohort patients).
[2] Reflects estimated LV Mass increase over 12-18M for DD patients based on retrospective natural history data-set (shown on slide 20).
Hughes 2008. Heart; Rettl 2022. EHJ CV Imaging; Solomon 2019. Circulation; Saberi 2021. Circulation

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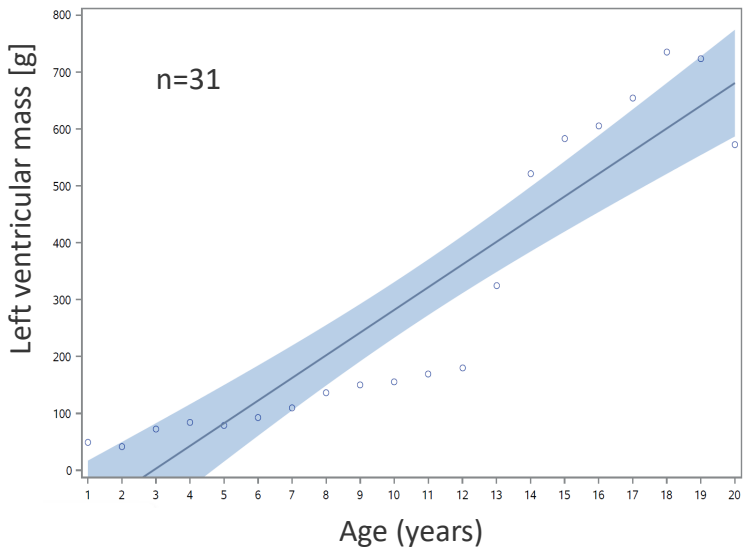
Cardiac Imaging Captures the Progression of Danon Disease

Significant Increases in LV Mass and LV Wall Thickness Correlate with Age

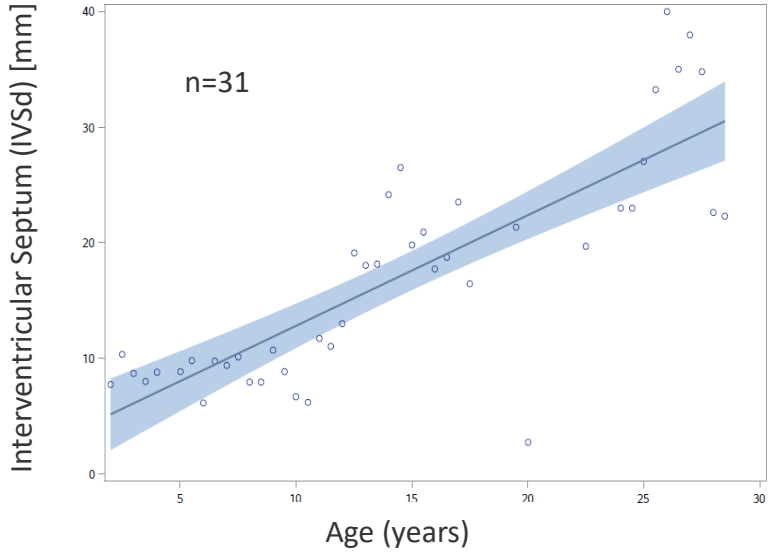
Trends in LV Mass

LV Mass increased by 39.86 ± 4.01 g per year



Trends in Septal Wall Thickness

Septal wall increased by 0.92 ± 0.15 mm/year



Data from the Natural History Studies demonstrated increases in key echo parameters in DD that are known to predict disease progression in other types of cardiomyopathy

* Unpublished data from International Danon Disease Registry

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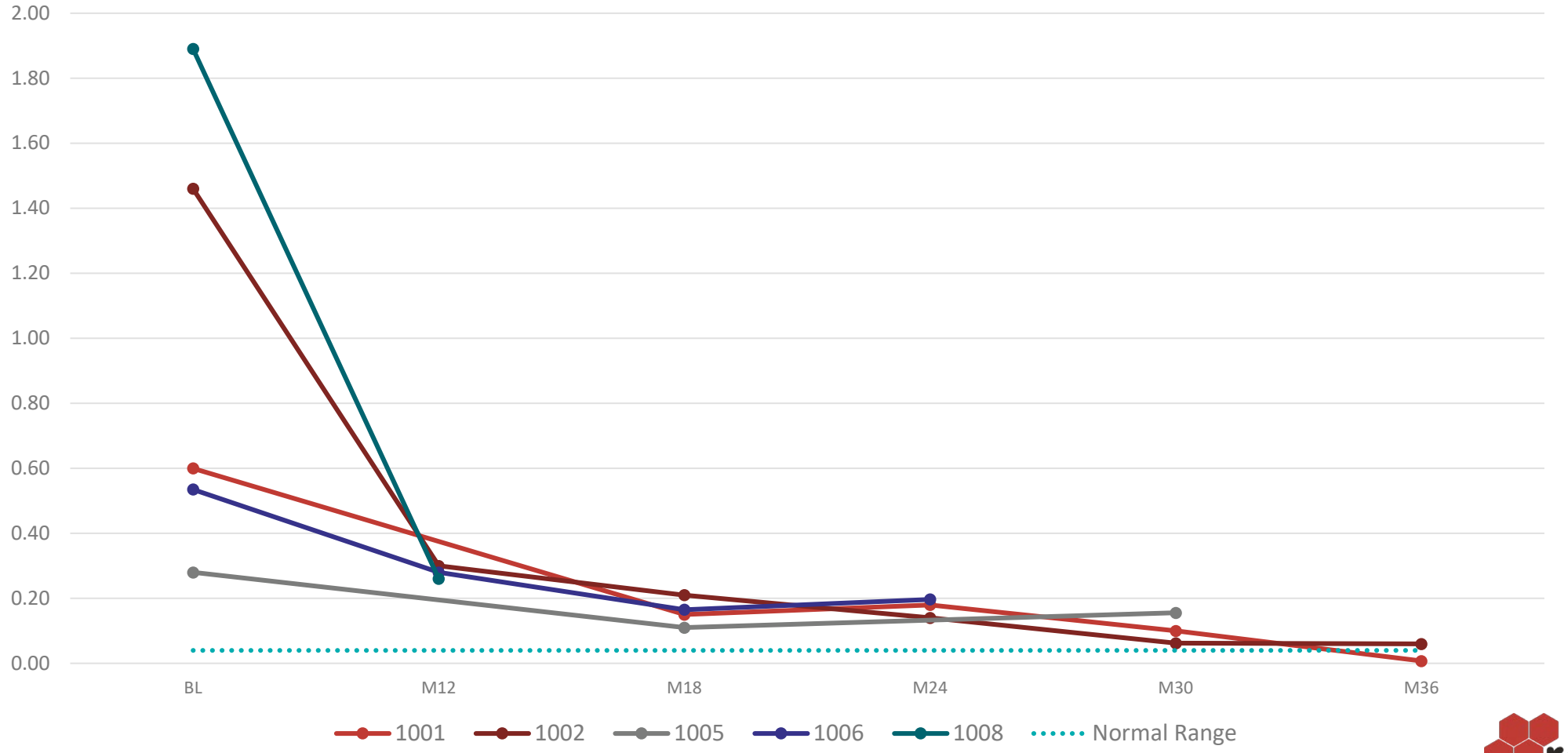
Significant and Sustained Reduction in Troponin (Key Secondary Endpoint) Observed Across Patients in Phase 1 Study

Phase 1 Trial: RP-A501 Treatment Conferred Improvement in Troponin-I Levels (ng/mL)



Note: Upper limit of normal 0.04 ng/mL, BL = baseline

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Current Status and Next Steps

rocket pharma

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Ongoing Danon Global Phase 2 Study Activities

Global Phase 2 Study (N=12)

United States

- ✓ RMAT, Fast Track, Orphan Drug Designations
- ✓ IRB approval at UCSD, CHOP; sites activated
- ✓ Multiple GMP lots manufactured in-house; sufficient drug product produced for full pivotal trial
- ✓ Global natural history study underway
  - ✓ FDA alignment on design
- ✓ Initiated pediatric safety run-in

Europe (UK + EU)

- ✓ Key regulatory designations obtained:
  - ✓ PRIME Designation
  - ✓ Orphan Drug Designation
  - ✓ Advanced Therapy Medicinal Product
- ✓ Scientific Advice Meeting held with EMA
  - ✓ On track for CTA/IMPD filing
- ✓ Multiple EU clinical site startup activities underway
- ✓ Successful QP audit of Rocket manufacturing facility; drug product cleared for EU use

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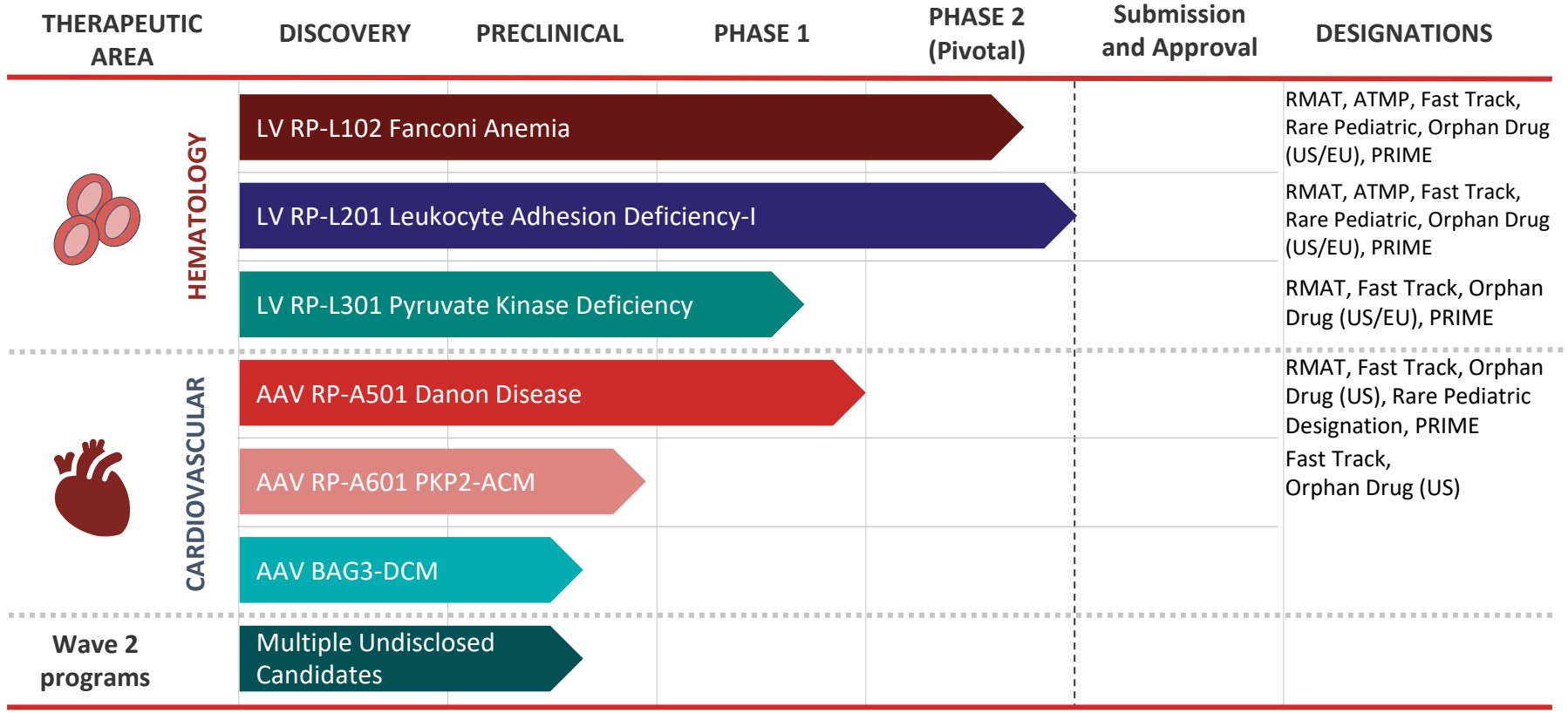
Rocket Pipeline: 6 Disclosed Programs Across Two Platforms with Compelling Clinical and/or Pre-clinical Proof of Concept

Criteria used to select programs

- First-, best- and/or only-in-class
- On-target MOA; clear endpoints
- Sizeable market to maximize patient impact

6+ programs with 2 programs fast approaching commercialization



AAV, adeno-associated virus; ATMP, advanced therapy medicinal product; BLA, Biologics License Application; LV, lentiviral vector; MAA, Marketing Authorisation Application; MOA, mechanism of action; PRIME, PRIority MEdicines; RMAT, regenerative medicine advanced therapy. PKP2: plakophilin 2; ACM: Arrhythmogenic Cardiomyopathy; BAG3: BLC2-associated athanogene 3 DCM: Dilated Cardiomyopathy

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