



SEEKING GENE THERAPY CURES

November 2024



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Vision: Seeking Gene Therapy Cures



Values

Trust

Curiosity

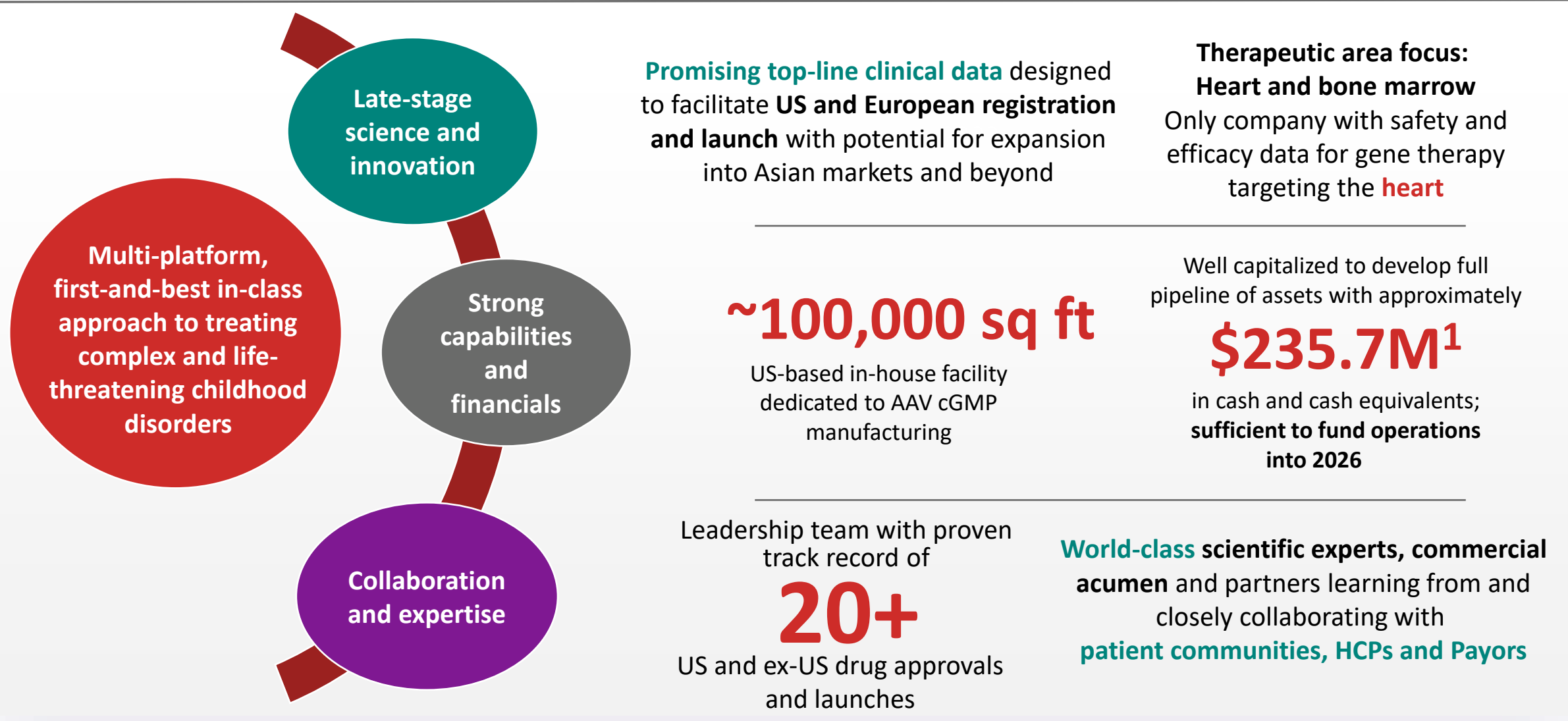
Elevate

Generosity

Mission

To develop **first-in-class** and **best-in-class curative gene therapies** for patients with devastating diseases

A Fully Integrated Gene Therapy Company



Strong Science, Carefully-selected Assets and Smart Execution

Criteria used to select programs



First-, best- and/or only-in-class

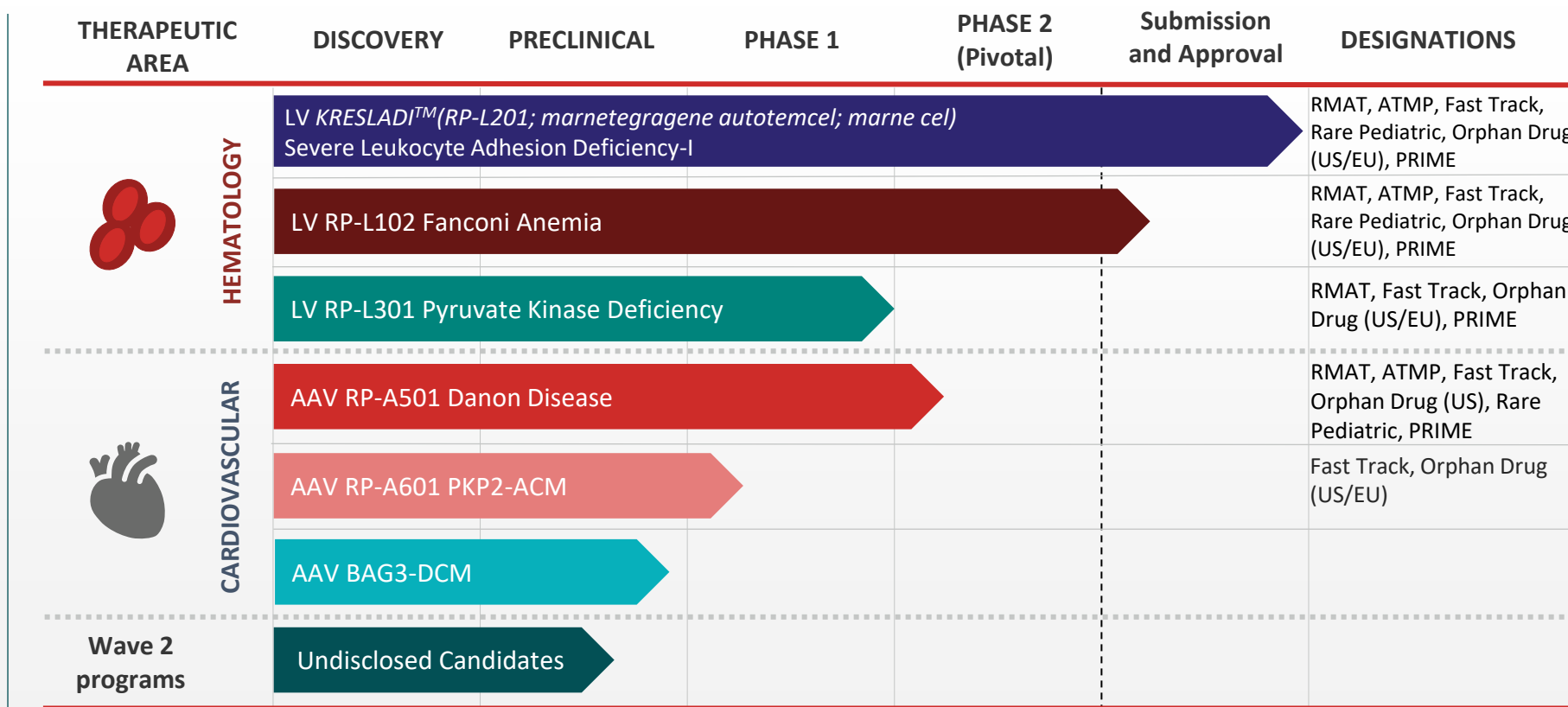


On-target MOA; clear endpoints



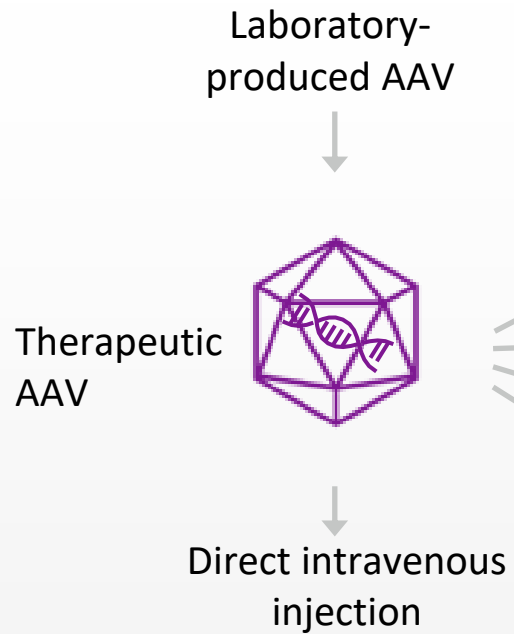
Sizeable market to maximize patient impact

6+ programs with 2 programs fast approaching regulatory filing and launch



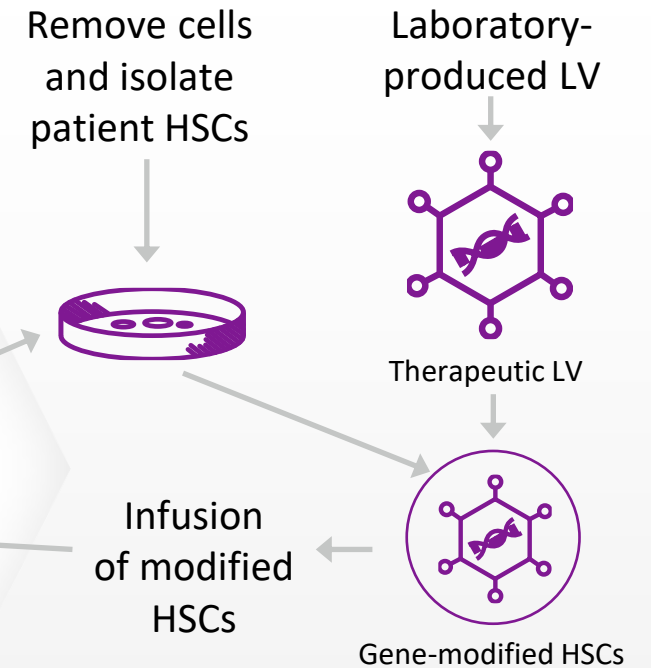
Rocket Offers Multi-platform Gene Therapy Expertise

IN VIVO platform



- RP-A501: Danon Disease
- RP-A601: PKP2-ACM
- AAV BAG3-DCM

EX VIVO platform



- RP-L102: Fanconi Anemia
- RP-L201: Leukocyte Adhesion Deficiency-I
- RP-L301: Pyruvate Kinase Deficiency

All Rocket therapies transfer full (non-truncated) coding sequence to target tissue

Rare Diseases Are Associated With a Reduced Lifespan¹



400 million

people globally are affected by a rare disease¹



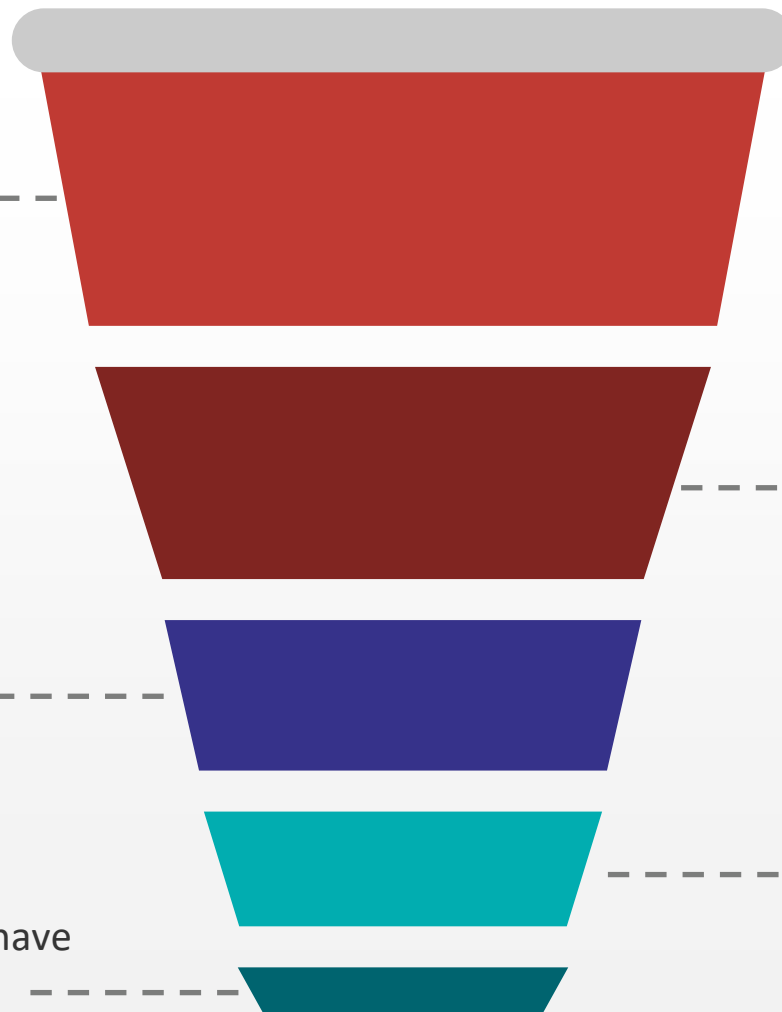
Children account for

50%

of rare disease patients¹



Only about 5% of rare diseases have an FDA-approved drug treatment¹



80% of rare diseases have monogenic origins¹

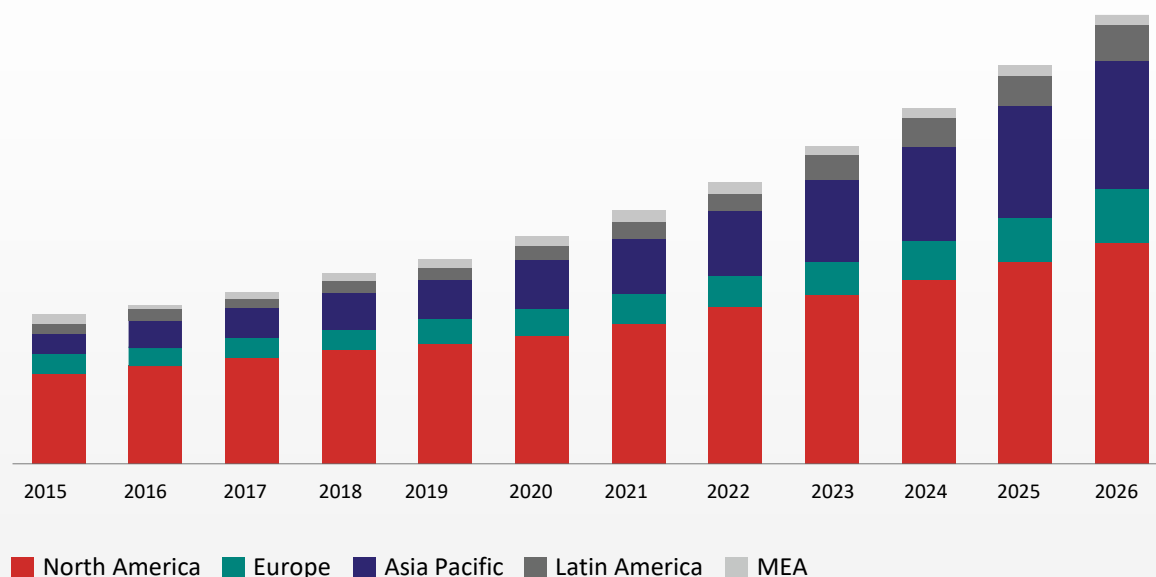


3 of 10 children with a rare disease die before their fifth birthday¹



Market for Rare Disease Treatment is Rising

Rare disease treatment market by region, 2015-2026 (USD million)¹



Rare disease treatment market by drug type, 2019 (USD million)¹



■ Biologics ■ Non-biologics

- Rare disease treatment market is projected to grow from **\$161.4 billion in 2020** to **\$547.5 billion by 2030²**
- CAGR of 13.1% projected by 2030²



Orphan drug approvals have increased

4-fold³

CAGR, compound annual growth rate.

1. Global Market Insights. Accessed April 2022. <https://www.gminsights.com/industry-analysis/rare-disease-treatment-market> 2. Global News Wire. Accessed August 2022. <https://www.globenewswire.com/en/news-release/2021/02/24/2181634/0/en/Global-Rare-Disease-Market-is-estimated-to-be-US-547-5-billion-by-2030-with-a-CAGR-of-13-1-during-the-forecast-period-by-PMI.html> 3. AHIP. Accessed April 2022. <https://www.ahip.org/how-big-pharma-makes-big-profits-on-orphan-drugs> (increase from 1998 to 2017)

Costs Associated With Rare Diseases Have Increased Exponentially¹

Economic impact¹



26-fold increase in average per-patient annual cost for orphan drugs* compared to doubled costs for specialty and traditional drugs¹

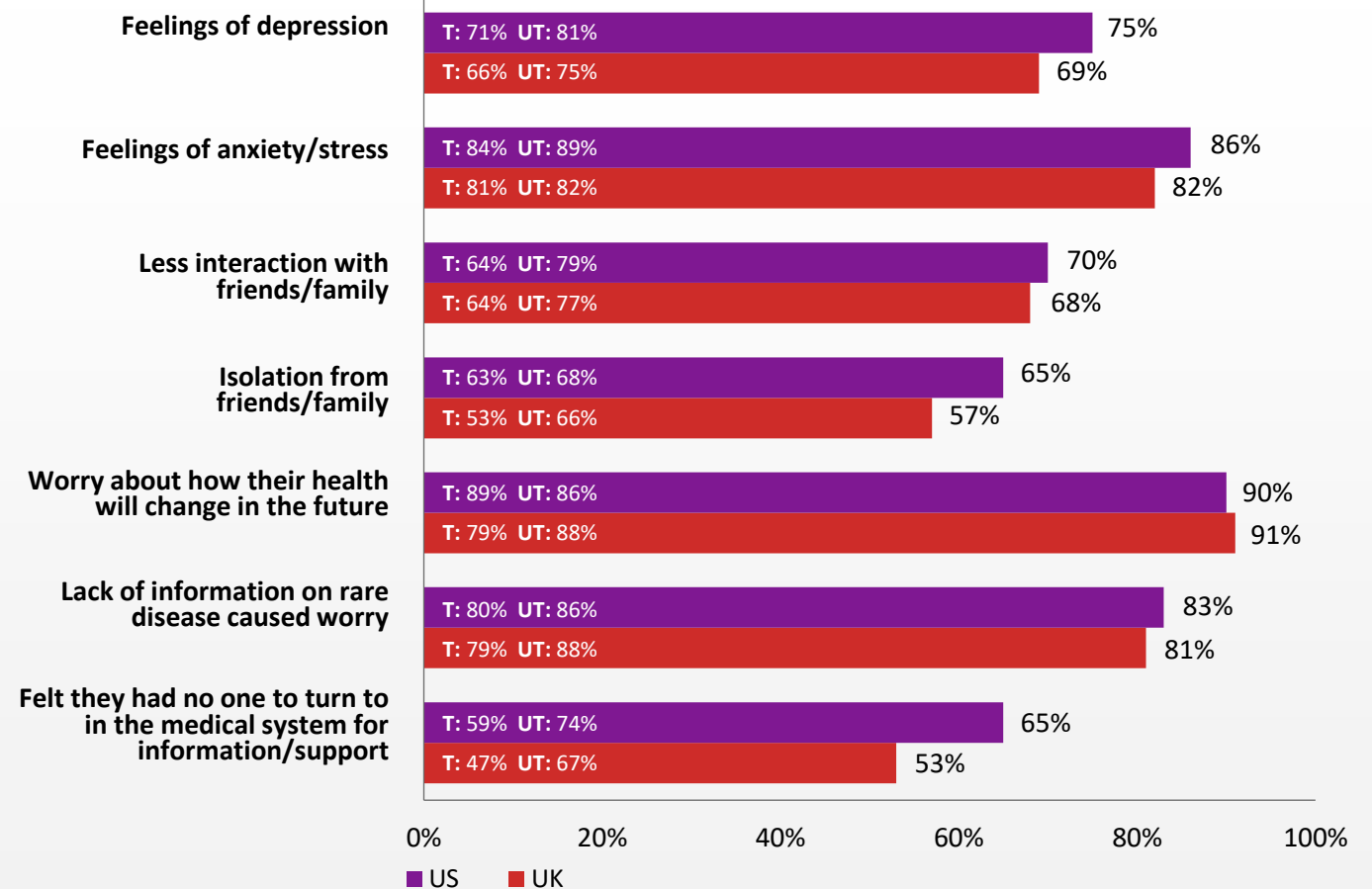


Patients with rare diseases or their caregivers are often compelled to leave the workforce²



Cost of bone marrow and heart transplants & maintenance is high

Emotional impact³



*An orphan drug is a pharmaceutical agent developed to treat medical conditions, which, because they are so rare, would not be profitable to produce without government assistance.

T, treatable; UT, untreatable.

1. AHIP. Accessed April 2022. <https://www.ahip.org/news/press-releases/drug-prices-for-rare-diseases-skyrocket-while-big-pharma-makes-record-profits> (increase from 1998 to 2017)

2. Every Life Foundation for Rare Diseases. Accessed April 2022. https://everylifefoundation.org/wp-content/uploads/2021/02/The_National_Economic_Burden_of_Rare_Disease_Study_Summary_Report_February_2021.pdf

3. Global Genes. Accessed April 2022. <https://globalgenes.org/wp-content/uploads/2013/04/ShireReport-1.pdf>

Danon Disease: Serious Condition with High Unmet Medical Need



Disease Etiology

- X-linked, dominant, monogenic disease
- Loss-of-function mutations in *LAMP2*



Therapeutic Challenges

- Standard of care:
 - Heart transplant
- Limitations:
 - Considerable morbidity and mortality
 - Only ~20% of patients receive HTx²
 - 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^{2,3}
- Females: Delayed median presentation (~20 years later) due to additional X chromosome, highly morbid and fatal disorder^{2,3}

Market Opportunity¹ – US and 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; HTx, heart transplant.

1. Rocket Pharmaceuticals data on file

2. Boucek D, Jirikowic J, Taylor M. Natural history of Danon disease. *Genet Med*. 2011;13(6):563-568.

3. Brambatti M, Caspi O, Maolo A, et al. Danon disease: Gender differences in presentation and outcomes. *Int J Cardiol*. 2019;286:92-98.

RP-A501 Phase I Study: Sustained LAMP2 Expression in Cardiomyocytes

Durable myocardial LAMP2 protein expression seen in all patients

Myocardial LAMP2 Protein Expression

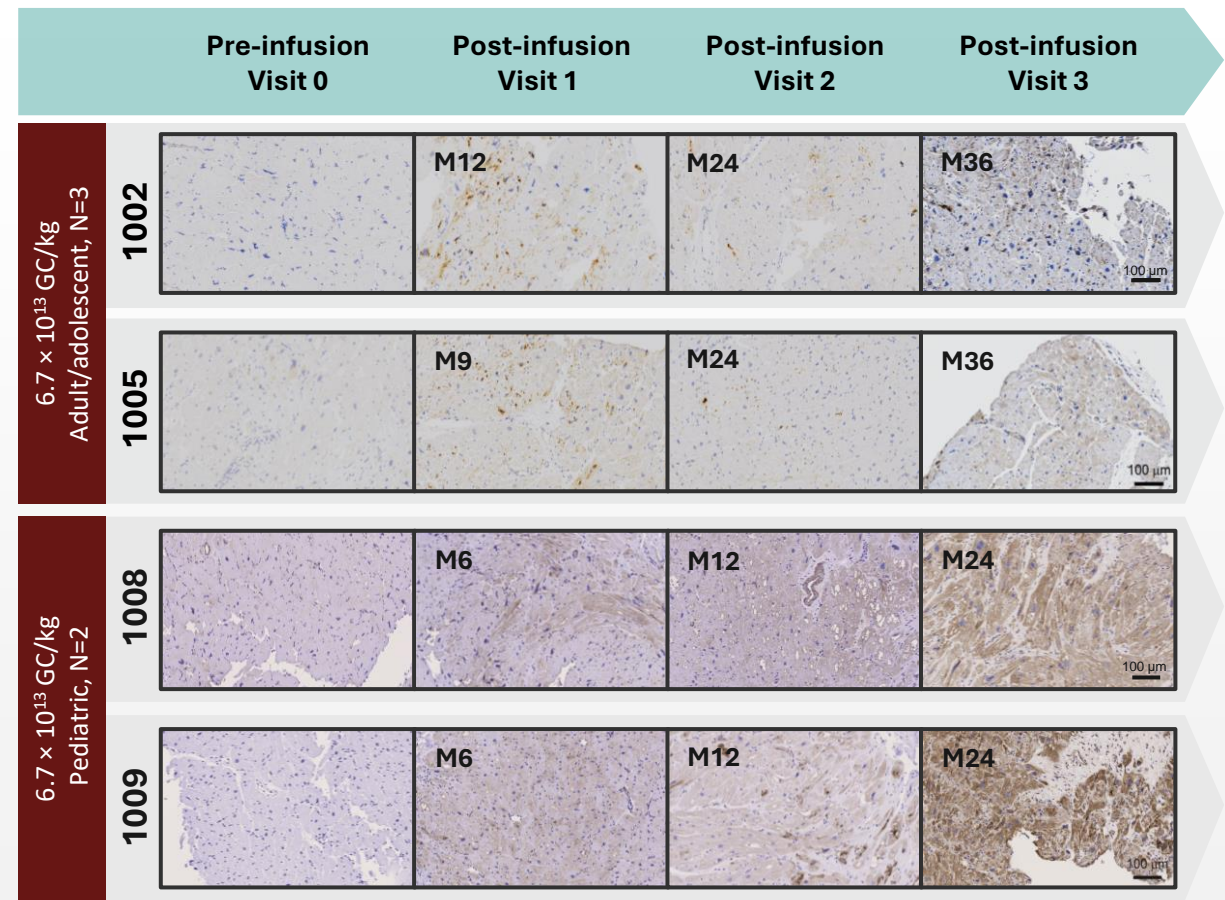
Cohort	Patient	BL	M6	M12	M18	M24	M30	M36	M60 [‡]
6.7 × 10 ¹³ GC/kg Adult/adolescent	1001	0	++	+	NP	NP	0*	0*	+++ [‡]
	1002	0	NP	+++	++	++	++	++	
	1005	0	NP	++ [†]	NP	+	+	+	
1.1 × 10 ¹⁴ GC/kg Adult/adolescent ^a	1006	0	+	+	+	+	NP	++	
6.7 × 10 ¹³ GC/kg Pediatric	1008	0	++	+	NP	++			
	1009	0	+	++	NP	+++			

[†]Reflects patient 1005 9M visit biopsy as 12M biopsy not performed
[‡] Preliminary assessment of biopsy from 1001 Y5 visit with updated IHC assay

Legend: IHC Staining Grade (% Positive Cardiomyocytes)

0 = no staining	+	= 1 (≤25%)	+++	= 3 (51%–74%)
NP = not performed	++	= 2 (26%–50%)	+++	= 4 (≥75%)

Representative LAMP2 IHC Images



a. Patient 1007 had LV systolic dysfunction (LVEF <40%) at enrollment and had progressive heart failure requiring transplantation 5m following RP-A501 treatment; this patient is currently stable 3 years post-transplant.

Note: Grading of LAMP2 protein expression by IHC was done by a board-certified pathologist in a blinded fashion. The semi-quantitative grading reflects the extent of LAMP2 protein expressing cardiomyocytes in the entirety of biopsy sample according to the scale: Grade 0, negative staining; Grade 1 = < 25%; Grade 2 = 26%-50%; Grade 3 = 51%-74%; Grade 4 = >75%.

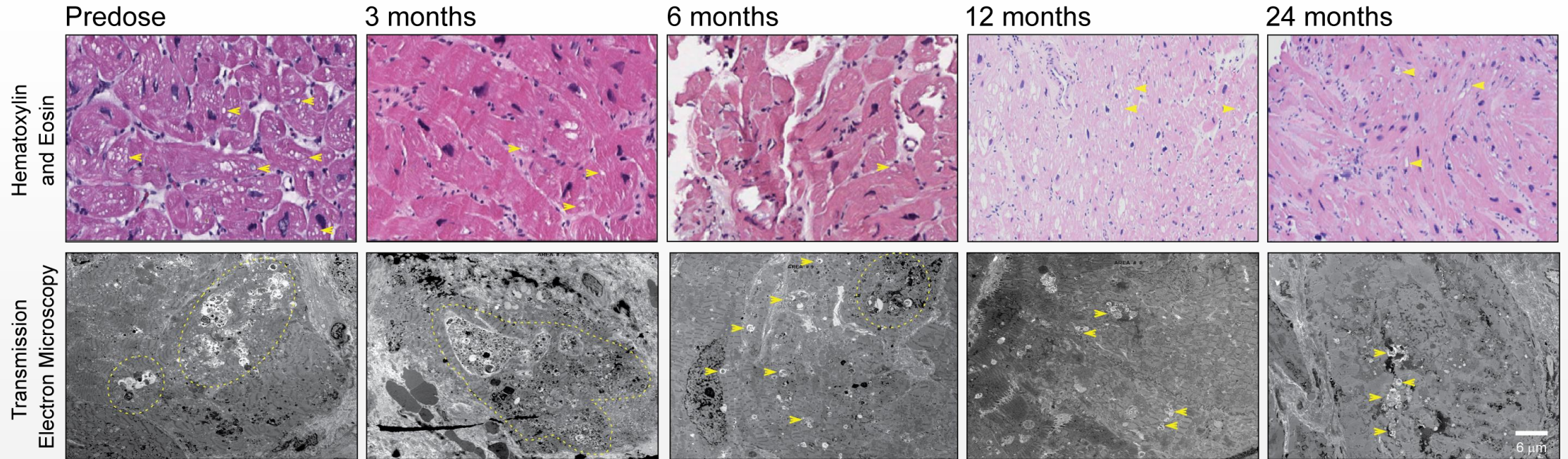
IHC=immunohistochemistry; LAMP2=lysosome-associated membrane protein 2; M=month(s); VCN=vector copy number.

*Patient 1001 demonstrated Grade 0 LAMP2 protein IHC staining at the 30- and 36- month assessments, however, patient 1001's LAMP2B vector RNA and DNA (VCN) levels have persisted through 36 months of follow-up.

RP-A501 Phase I Study: Decreased Cardiomyocyte Vacuolization

Enhanced autophagy leads to improved myocardial ultrastructure and clinical phenotype

Representative Images from the Endomyocardial Biopsy of Patient 1008



Dashed yellow lines mark myocardial regions with high densities of phagocytic vacuoles. Yellow arrowheads mark small clusters or individual phagocytic vacuoles

RP-A501 Phase I Study: Benefit Observed Across All Key Parameters

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

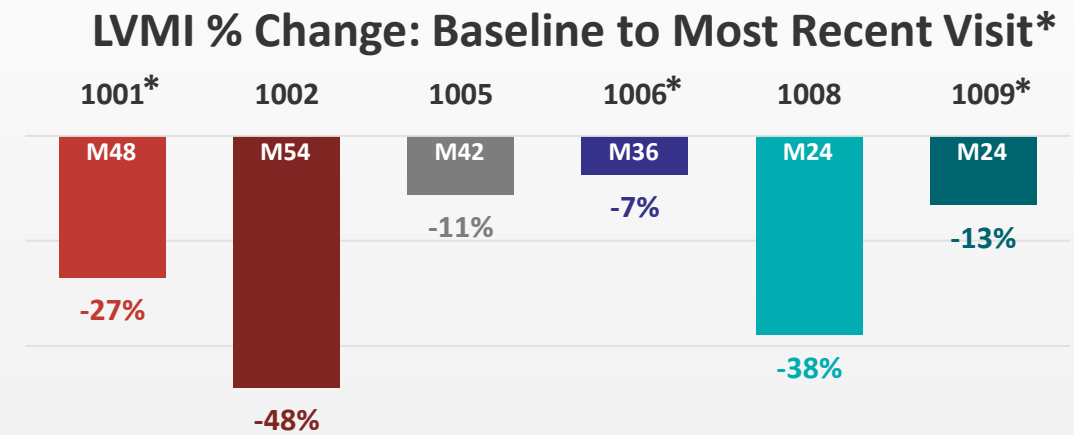
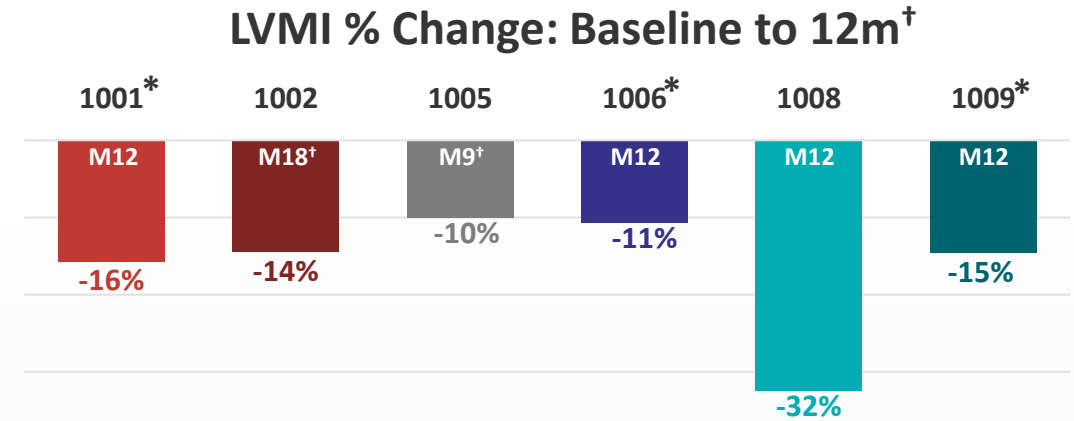
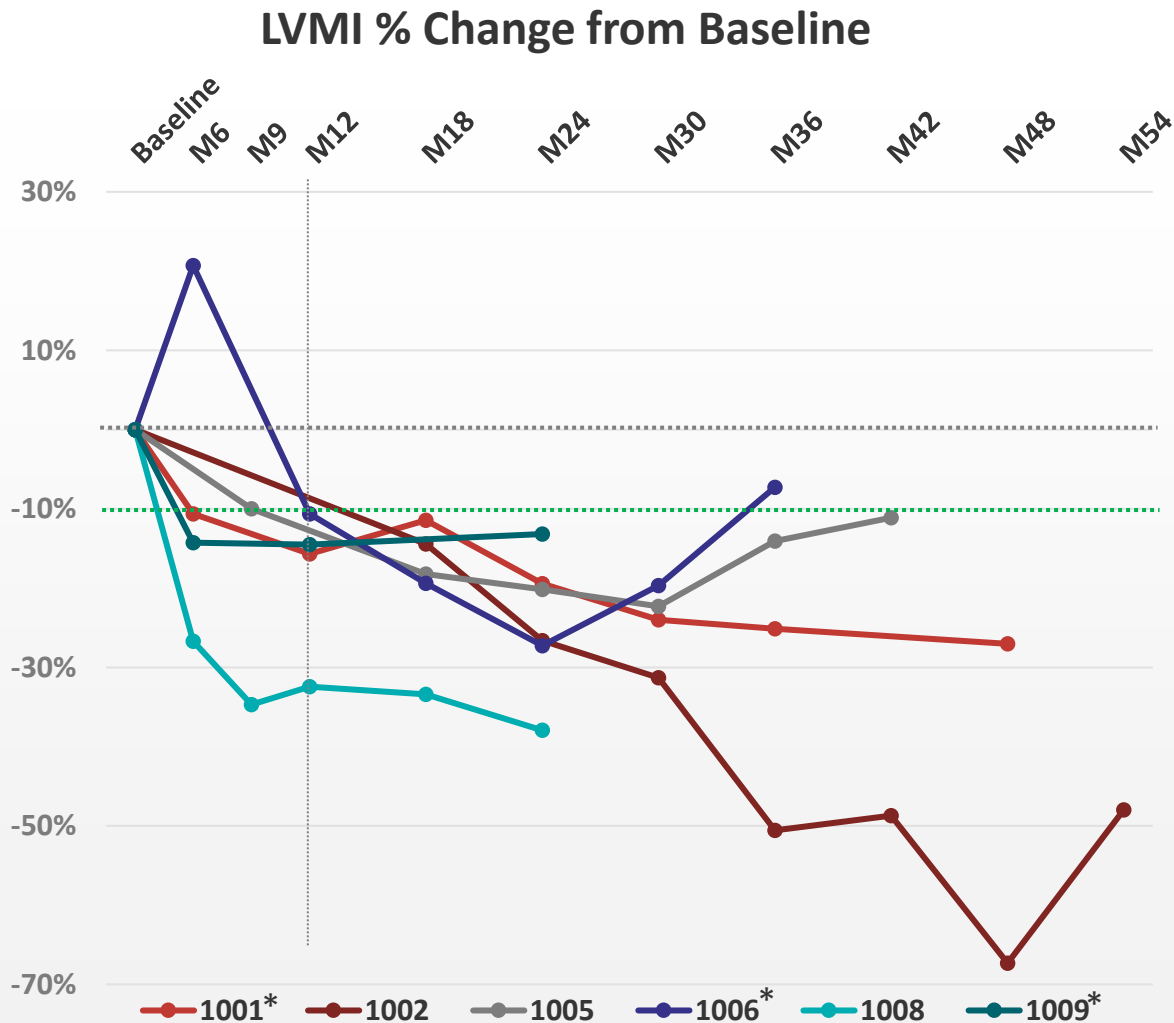
Cohort	Patient	Age at Most RV (y)	Most Recent Visit (mo)	LVEF BL to RV (%)	Δ LVMI,* BL to RV (g/m ^{2.7})	Δ IVSd, BL to RV (mm)	Δ LVPWd, BL to RV (mm)	Δ NT-proBNP, BL to RV (ng/L)	Δ cTnl,† BL to RV (ng/mL)	Δ NYHA Class	Δ KCCQ-12 OS, BL → RV
1:Low Dose Adult/ Adolescent	1001	22.3	54	57 to 64	-33%, 85 to 56.9	-6%, 19.8 to 18.6	-20%, 18.8 to 15	-17%, 336 to 279	-99% 0.6 to 0.01	II to I	+52, 44 to 96
	1002	24.9	54	55 to 66	-48%, 260.2 to 135.3	-52%, 60.1 to 28.6	-49%, 39.1 to 19.8	-93%, 5119 to 351	-96%, 1.46 to 0.06	II to I	+27, 64 to 91 [†]
	1005	21.8	42	65 to 59	-11%, 98.2 to 87.3	-10%, 30.9 to 27.8	-27%, 32.1 to 23.4	+16%, 841 to 975	-33%, 0.28 to 0.19	II to I	+7, 77 to 84
2:High Dose Adult/ Adolescent	1006	23.9	36	62 to 51	-7%, 68.6 to 63.6	+5%, 18.0 to 19.0	-27%, 24.0 to 17.4	-65%, 720 to 249	-39%, 0.47 to 0.29	II to I	+9, 79 to 89
3:Low Dose Pediatric	1008	14.4	24	74 to 78	-38%, 141.5 to 87.8	-19%, 42.4 to 34.2	+1%, 22.8 to 23.1	-78%, 1629 [‡] to 360 [‡]	-85%, 1.78 to 0.27	II to I	+27, 50 to 77
	1009	13.7	24	77 to 77	-13%, 82.0 to 71.2	+12%, 18.5 to 20.8	-3%, 14.9 to 14.4	-48%, 1912 to 998	-82%, 1.08 to 0.20	II to I	+30, 52 to 82

* Centrally evaluated (blinded) MRI data were utilized for LVMI when available. All other measurements of cardiac structure and function reflect centrally evaluated (blinded) echocardiogram data.

† Central laboratory assessment of cTnl were performed on cryopreserved and non-cryopreserved samples. Values for cTnl from high-sensitivity and earlier tests. high-sensitivity and earlier assay are expressed in ng/mL.

Improved (Green) Stabilized (Yellow) Worsened (Red)

RP-A501 Phase 1 Study: Sustained Improvements in LV Mass Index



All patients showed ≥10% LVMI decrease at ~12m; improved or sustained at most recent visit

* Where possible, cardiac MRI assessments shown (patients 1001, 1006, and 1009); otherwise, echocardiogram data presented. All assessments were conducted by a single reviewer blinded to both patient and timepoint, except for Patient 1001 cardiac MRI data, which includes reads from multiple reviewers. Patient 1001 most recent visit with MRI assessment was at 48m

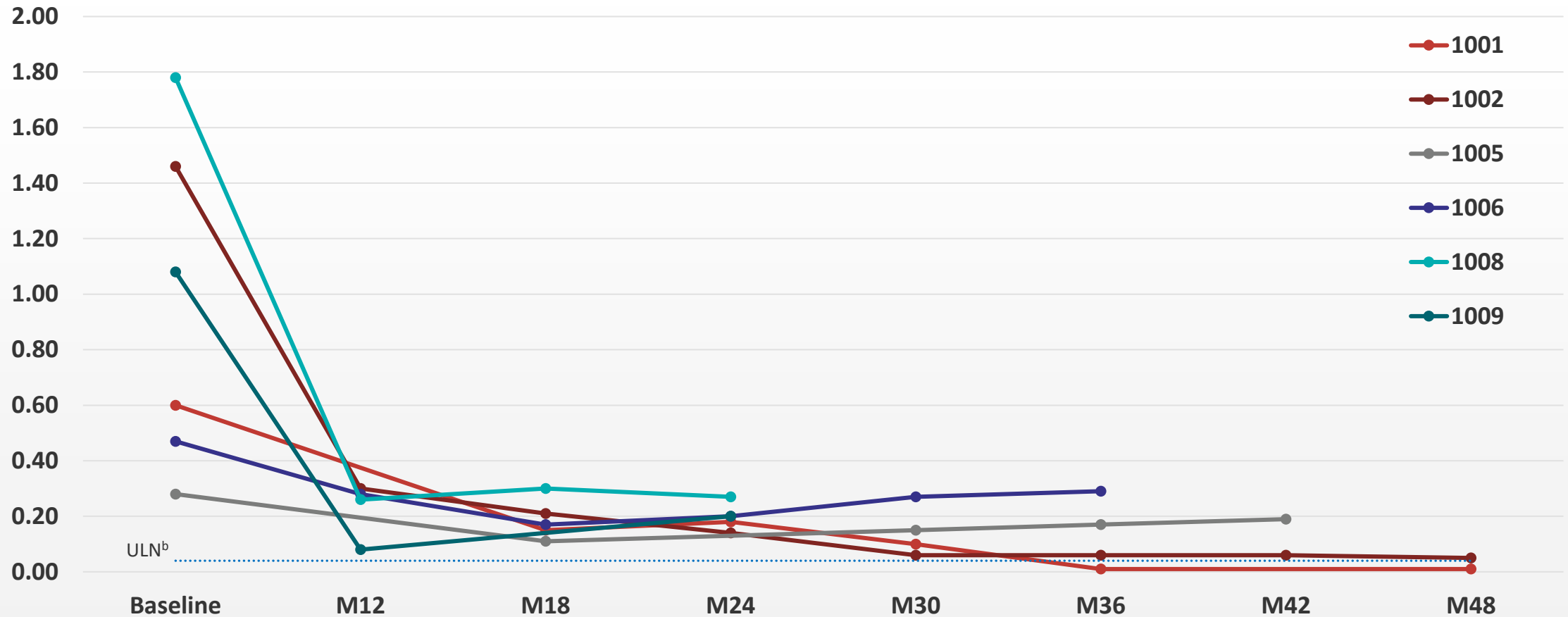
† Utilized 9m or 18 m data when 12m assessment was not done.

LVMI, left ventricular mass index; MRI, magnetic resonance imaging; m, month(s).

Data cut-off: April 19, 2024.

RP-A501 Phase 1 Study: Sustained Reductions in Cardiac Troponins

Cardiac Troponin-I Levels^a Pre- and Post-RP-A501 (ng/mL)



^aVisits not conducted, and results pending or unavailable at various timepoints; data shown are cTnI levels performed on high-sensitivity and older assays. Values from both assays are expressed in nanograms per milliliter for consistency.

^bRepresentative ULN: 0.04 ng/mL.

cTnI, cardiac troponin I; M, month(s); ULN, upper limit of normal.

Insights from Danon Disease Patients Treated on the Phase 1 Trial

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 to. Another amazing thing we have seen is about 4 months after his therapy trial he started working and stopped using his motorized scooter altogether. -Patient 1005

Prior to therapy, he would say "my wish is not to die young." After gene therapy, we see him smile more because he was able to hold down a steady part-time job and can live independently in an apartment of his own. He is living a life he didn't think would be possible.

-Patient 1006

He went to overnight summer camp on his own for the first time and is no longer out of breath walking up stairs.

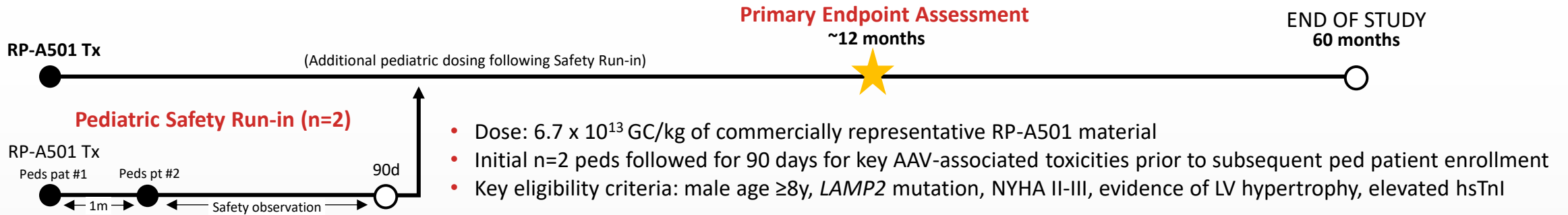
-Patient 1008

He is now able to exercise on a more regular basis. After treatment, he was able to participate in an organized walk with his father completing most of the 10K course. -Patient 1009

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

Pivotal, global, single-arm, open label study

PIVOTAL PHASE 2 STUDY DESIGN



CO-PRIMARY ENDPOINT (AA)

- LAMP2 protein \geq Grade 1 (IHC) AND
- Left Ventricular Mass: $\geq 10\%$ ↓

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

Primary Endpoint 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 model¹
- 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 factor²
- 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:

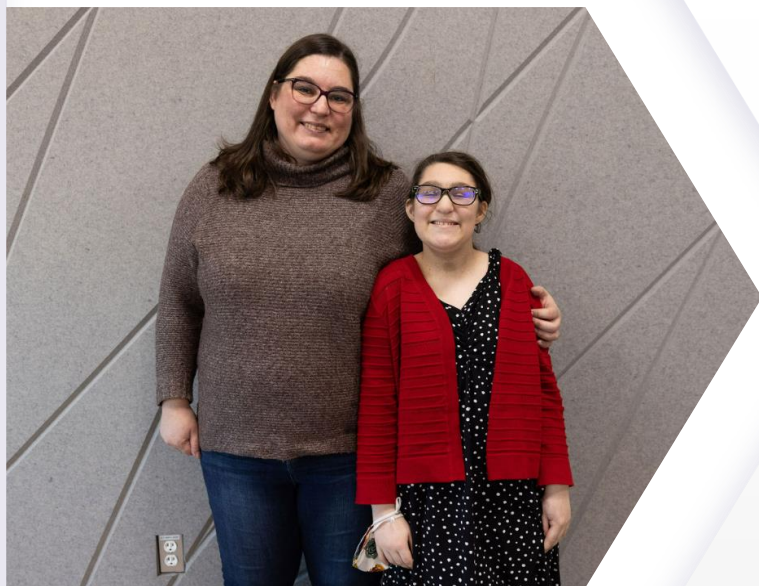
- *All components are measurable and unlikely to improve in the absence of a true treatment effect*
- *Primary endpoint will be assessed in the context of biomarkers, symptoms, QoL, clinical events derived from secondary endpoints and concurrent natural history study*
- *Phase 1 trial: LAMP2 expression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

In-House Manufacturing to Support Danon Pivotal Study and Commercial Production

- **2 Successful Danon AAV cGMP batches produced in Q4 2022**
- **Superior specifications to Phase I material**; allow for full dosing with lower total viral particles, potentially further improving safety profile
 - *Productivity*: ~3X increase in number of patient treatments per batch
 - *Product Quality*: Significant increase in full versus empty viral particles
 - *Product Comparability*: All attributes tested to date are comparable or improved
- **Regulatory progress and production capacity can support pivotal study and commercialization**
 - FDA clearance on continued utilization of HEK-293 cell-based process through commercial
 - FDA alignment on comparability approach
 - Potency assay developed in-house

Overall, in-house cGMP manufacturing delivers commercial-ready product with higher yield, improved quality, and potential for enhanced safety profile

RP-L102 for Fanconi Anemia Complementation Group A



Fanconi Anemia (A, C, and G)

Market Opportunity¹ – US and EU

Prevalence of **5,500 to 7,000** individuals

Annual incidence of **200 to 275** individuals



Disease etiology

- FA-A is an autosomal recessive disease caused by *FANCA* gene mutations
- FA proteins enable DNA repair
- FA-A accounts for **60% to 70%** of FA cases



Therapeutic challenges²

Standard of care:

- Allogeneic HSCT

Limitations:

- Significant toxicities, especially for patients who do not have an HLA-identical sibling donor (~80%)
- 100-day mortality
- GvHD
- Increased long-term cancer risk



Clinical manifestations

Disorder of DNA repair characterized by:

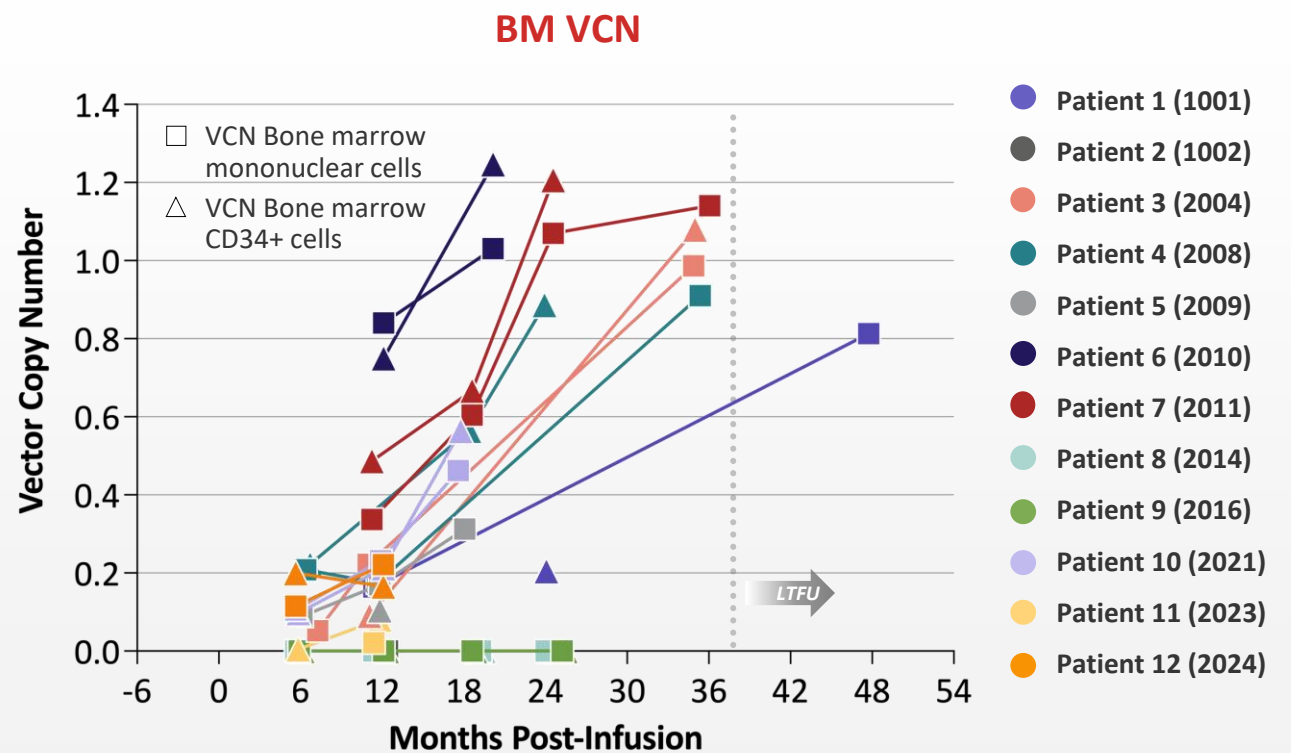
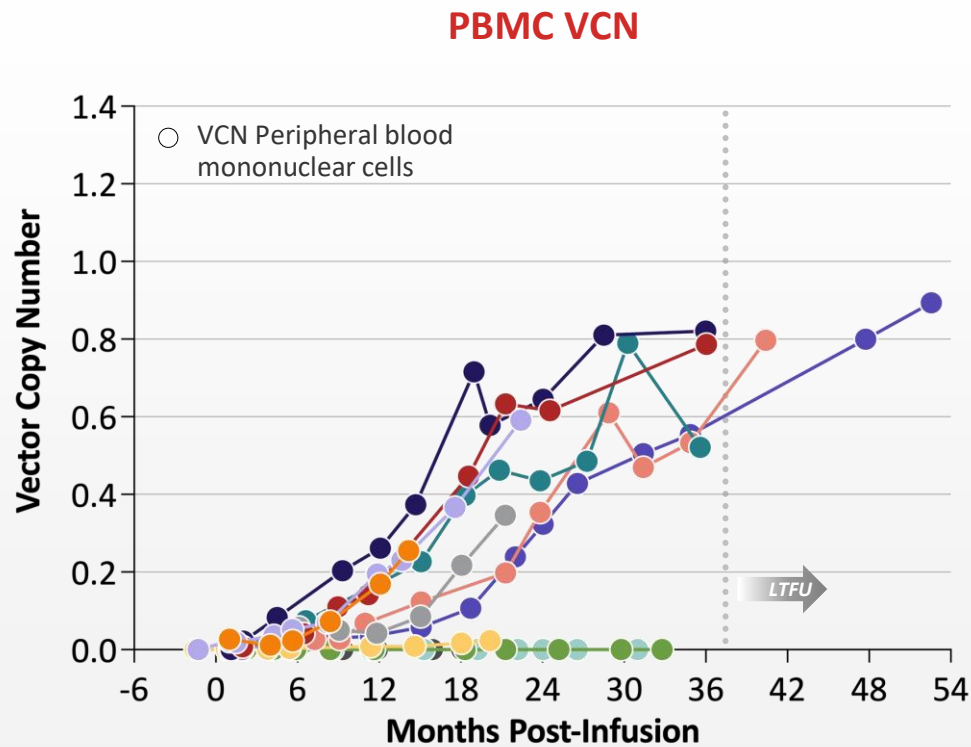
- Progressive BMF; 80% of patients experience BMF within first decade of life³
- Predisposition to hematologic malignancies and solid tumors

*Gene therapy approach: Selective advantage of corrected cells allows for **ex-vivo LV therapy without conditioning**; highly favorable benefit risk profile*

Progressively Increasing and Sustained Genetic Correction in 8 of 12 Patients ≥ 1 Year Post-RP-L102 in Pivotal Phase 2 Trial



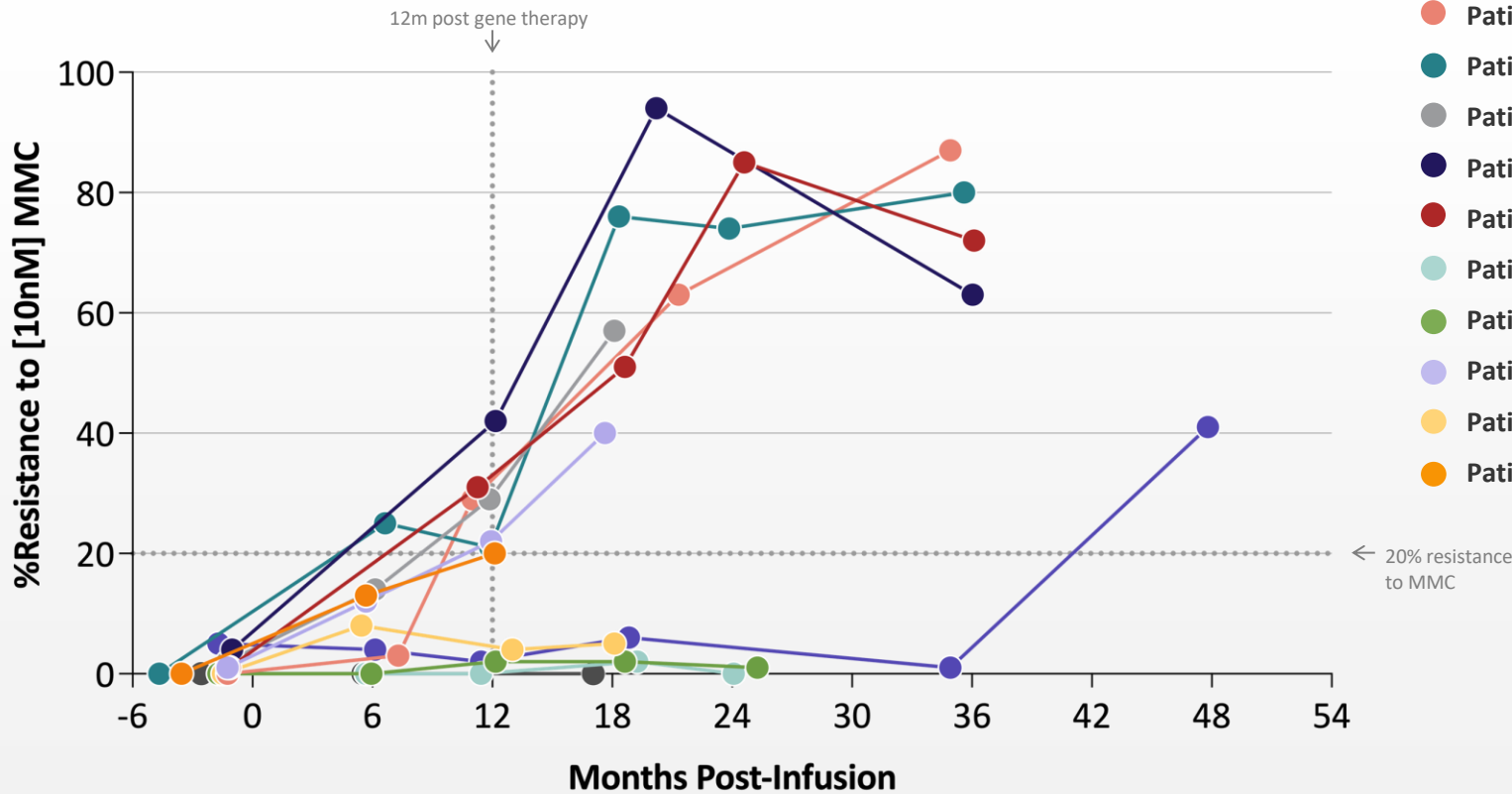
Progressive increases in PB and BM gene marking in 8 patients



Increasing Phenotypic Correction over 1 to 3 Years Post RP-L102 in Pivotal Phase 2 Trial



BM MMC-resistance $\geq 20\%$ at 12m in 7 of 12 patients
Sustained BM MMC-resistance confirmed in 6 patients *



7 of 12 patients had MMC-resistance of $\geq 20\%$ at 12 months

For 6 patients, increased MMC-resistance in BM CFU (40% to 94%) was observed 18 to 24 months post RP-L102
(confirmatory assessment pending for patient 12)

BM, bone marrow; CFU, colony-forming units; MMC, mitomycin-C.
 *One additional patient (Patient 1: 1001) was noted to have BM MMC resistance of 49% at ~40 months post-RP-L102 infusion (Unscheduled visit, not shown) and ~41% at 48 months post-RP-L102 infusion. Data cut-off: September 11, 2023; Preliminary interim results are presented from the ongoing clinical studies.

Development Plan



Moving toward BLA/MAA submission

INITIAL EFFICACY AND HIGHLY FAVORABLE SAFETY PROFILE

- 7 of 11 patients evaluable for efficacy are clinical therapeutic successes based on ≥ 18 months of data.*
- No cytotoxic conditioning, only 1 transient RP-L102 related SAE (Grade 2)

TOP-LINE DATA READOUT ACHIEVED

- Met clinical criterion of at least 5 patients achieving primary composite endpoint, including BM MMC resistance at least 20% at 12 months and confirmed at 18- or 21-months post-infusion.*

NEXT STEPS

- MAA submission accepted – under review
- Initiated Rolling BLA with the FDA

Additional life-cycle management activities:

- Expansion to FANC C and G
- Exploration of non-genotoxic conditioning and HSC expansion

REGULATORY DESIGNATIONS:

- RMAT and PRIME
- Orphan Drug designation in the US and EU
- Rare Pediatric Disease designation (eligible for PRV)
- Fast Track (US), ATMP

RP-L201 for LAD-I: *ITGB2* Gene Mutation



Market Opportunity¹ – US and EU

Prevalence of **800 to 1,000** individuals

Annual incidence of **50 to 75** individuals



Disease etiology

- *ITGB2* gene mutations (21q22.3), encoding the beta-2-integrin, CD18; essential for leukocyte adhesion to endothelium
- CD18 absent or reduced on neutrophils



Therapeutic challenges

Standard of care:

- Allogeneic HSCT

Limitations:

- Donor availability
- Infections
- Frequent GvHD
- Graft failure



Clinical manifestations

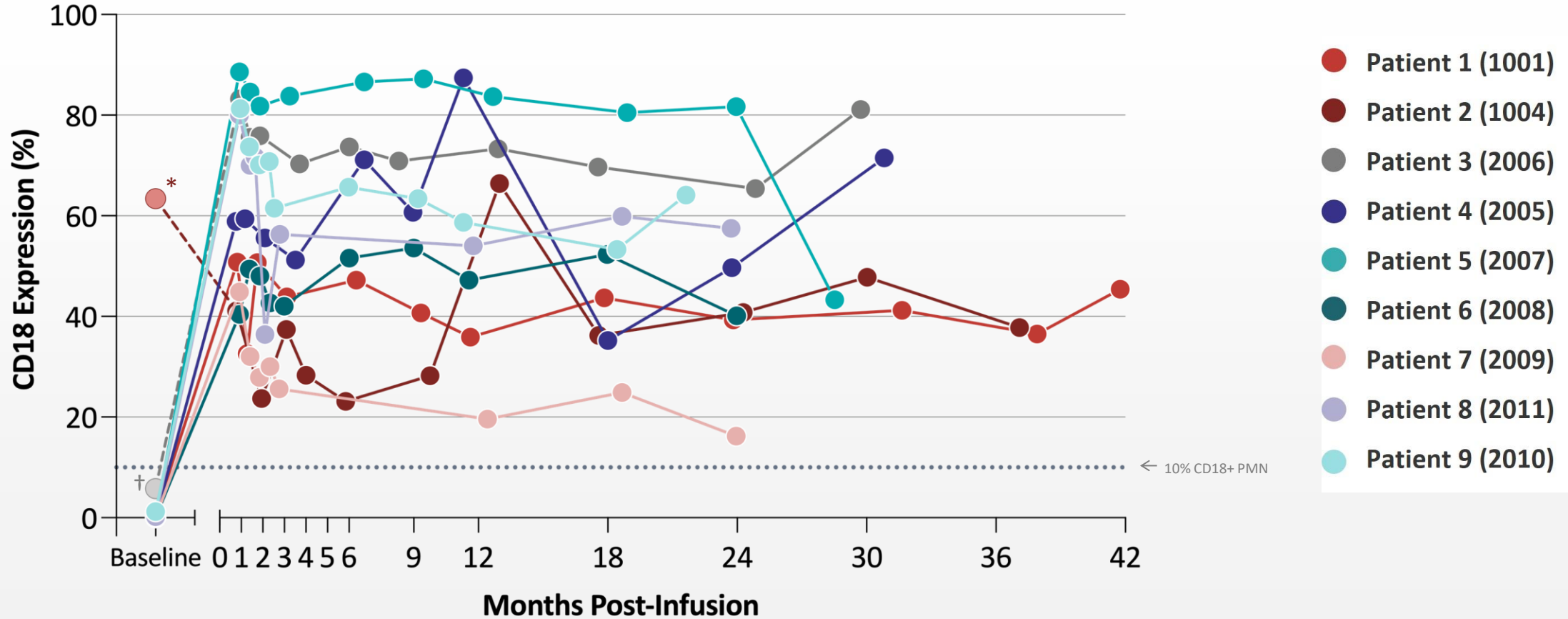
Patients suffer from recurrent infections; fatal in majority²

- Severe LAD-I: Death prior to age 2 in 60% to 75% of patients, infrequent survival >5 years in absence of allogeneic HSCT
- Moderate LAD-I: Death prior to age 40 in >50% of patients, extensive morbidity with recurrent infections and inflammatory lesions

CD18 Expression in PB Polymorphonuclear Cells in Pivotal Phase 1/2 Trial



Sustained >10% PMN CD18 expression 1 year after gene-corrected cell infusion across the entire cohort



Neutrophil CD18 expression is reported utilizing CD18 monoclonal antibody (clone 6.7).

* Dim/weak CD18 expression reported at baseline for Patient 2 (1004) in ~63% of cells in conjunction with <2% CD11a/CD11b expression, likely indicating abnormal/unstable protein.

† Dim/weak CD18 expression reported at baseline for Patient 3 (2006) in ~5.8% of cells in conjunction with <2% CD11a/CD11b expression, likely indicating abnormal/unstable protein.

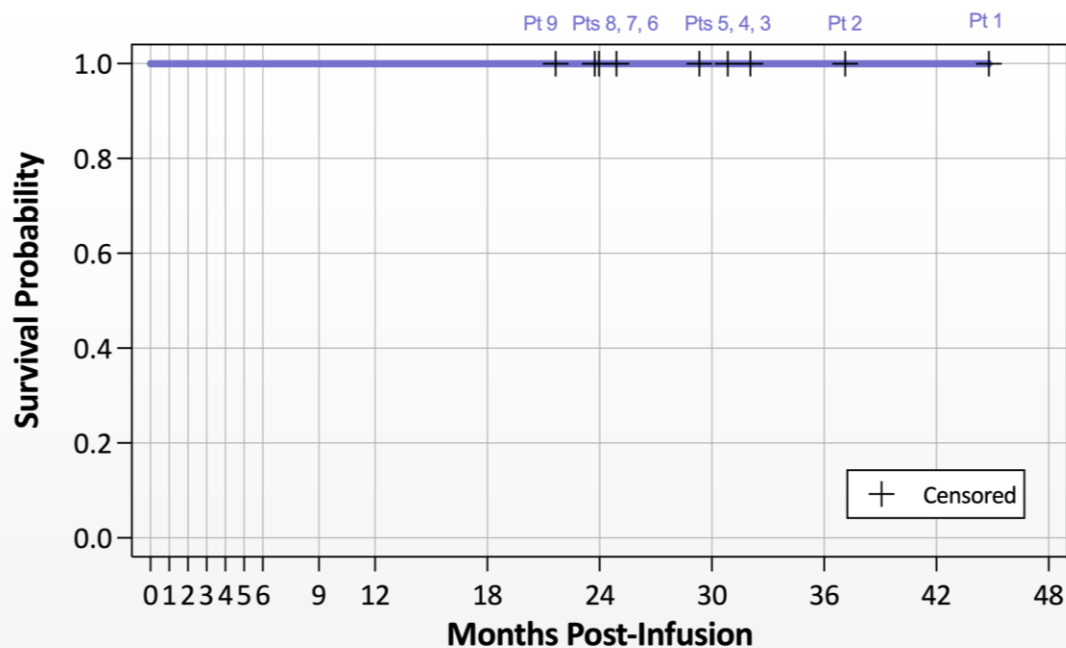
PB, peripheral blood; PMN, polymorphonuclear neutrophil.

Data on file. Rocket Pharmaceuticals. 2024. Data Cut-Off: July 24, 2023. RP-L201-0318 120-Day Efficacy Update.

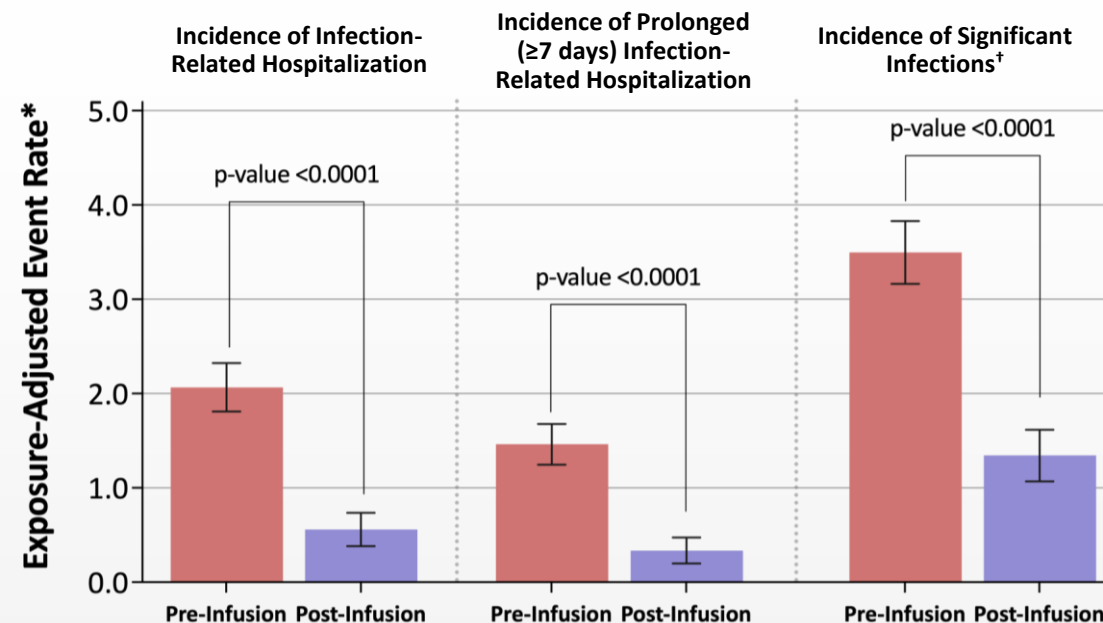
Pt 5 (2007) VCN at 30m timepoint remained stable relative to prior months, consistent with aberrant (artificially low) CD18 result.

Significant Reduction in Hospitalizations and 100% HSCT-free Survival in Pivotal Phase 1/2 Trial

100% HSCT-free survival Kaplan–Meier estimate



Meaningful reduction in infection-related hospitalizations following immune reconstitution



Survival without allogeneic HSCT

Primary outcomes

- ≥1-year post–RP-L201 infusion AND
- ≥2 years of age for subjects enrolled <1 year of age

- *Infections that developed beyond 90 days post-infusion were consistent with typical childhood infections frequently observed in immunocompetent (healthy) children*
- *All patients have been able to stop prophylactic antibiotics (when permitted by institutional policy)*

* Annualized event rate is calculated as the Total Number of Events / Total Time in each Time Period. Results are adjusted event rate per year. Pre-infusion includes all lifelong medical history prior to RP-L201 infusion. p-values from Poisson regression with event and time period in the model with an offset of log exposure.

† Significant infections are defined as those requiring hospitalization or I.V. antimicrobial therapy.

HSCT, hematopoietic stem cell transplantation. Data Cut-Off: July 24, 2023; RP-L201-0318 120-Day Efficacy Update.

Development Plan



Moving toward product filing

ENROLLMENT AND INITIAL EFFICACY

- Enrollment completed; 9/9 patients treated
- Efficacy observed in 9/9 patients with 12 to 36 months follow-up
- Efficacy is comprehensive, across all efficacy parameters including CD18 expression and survival

TOP-LINE DATA READOUT Q2 2022

- Survival for 9/9 patients, ≥ 2 years age and ≥ 1 year post-treatment
- No graft failure, GvHD
- No RP-L201 related SAEs

NEXT STEPS

- FDA Approval
- Establish therapy as a safe and effective treatment option for LAD-I patients
- Create a commercial infrastructure that can be leveraged for future programs and franchises

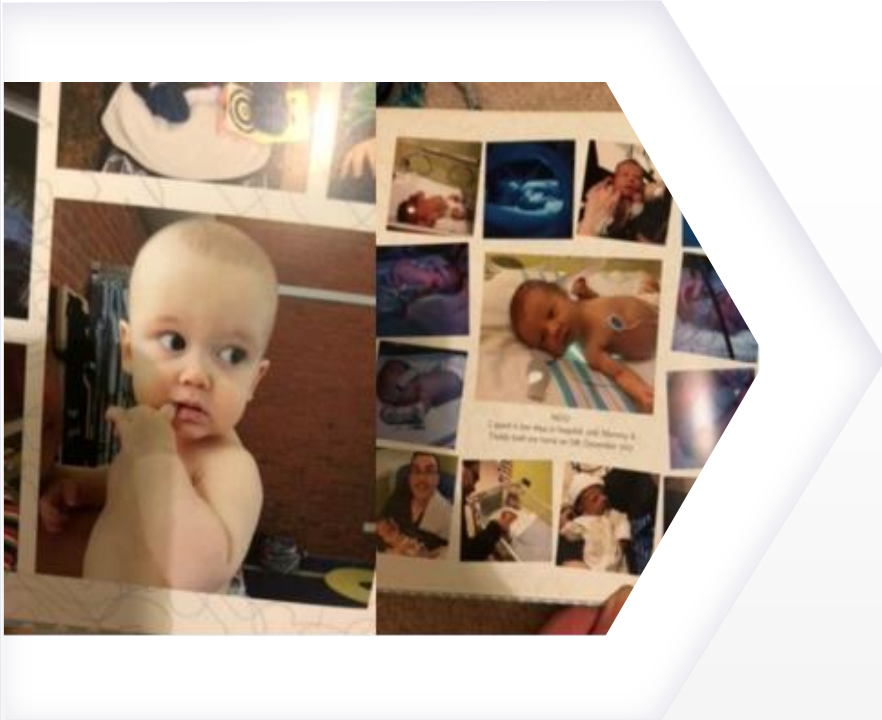
Life-cycle management

- Potential label expansion to include moderate LAD-I population

REGULATORY DESIGNATIONS:

- RMAT and PRIME
- Orphan Drug designation in the US and EU
- Rare Pediatric Disease designation (eligible for PRV)
- Fast Track (US), ATMP

RP-L301 for PKD: *PKLR* Gene Mutation



Disease etiology²

- Autosomal recessive inheritance
- Pyruvate kinase deficient RBCs cannot synthesize ATP, resulting in hemolytic anemia



Therapeutic challenges³

- Standard of care: Chronic blood transfusions and splenectomy
- Limitations:
 - Iron overload
 - Extensive end-organ damage
 - Splenectomy confers lifelong infection and thrombotic risk



Clinical manifestations⁴

- Lifelong chronic hemolysis
- Other clinical manifestations:
 - Anemia
 - Jaundice
 - Iron overload

Market Opportunity¹ – US and EU

Prevalence of **4,000 to 8,000** individuals

Annual incidence of **75 to 125** individuals

ATP, adenosine triphosphate; PKD, pyruvate kinase deficiency; PKLR, pyruvate kinase L/R; RBC, red blood cell.

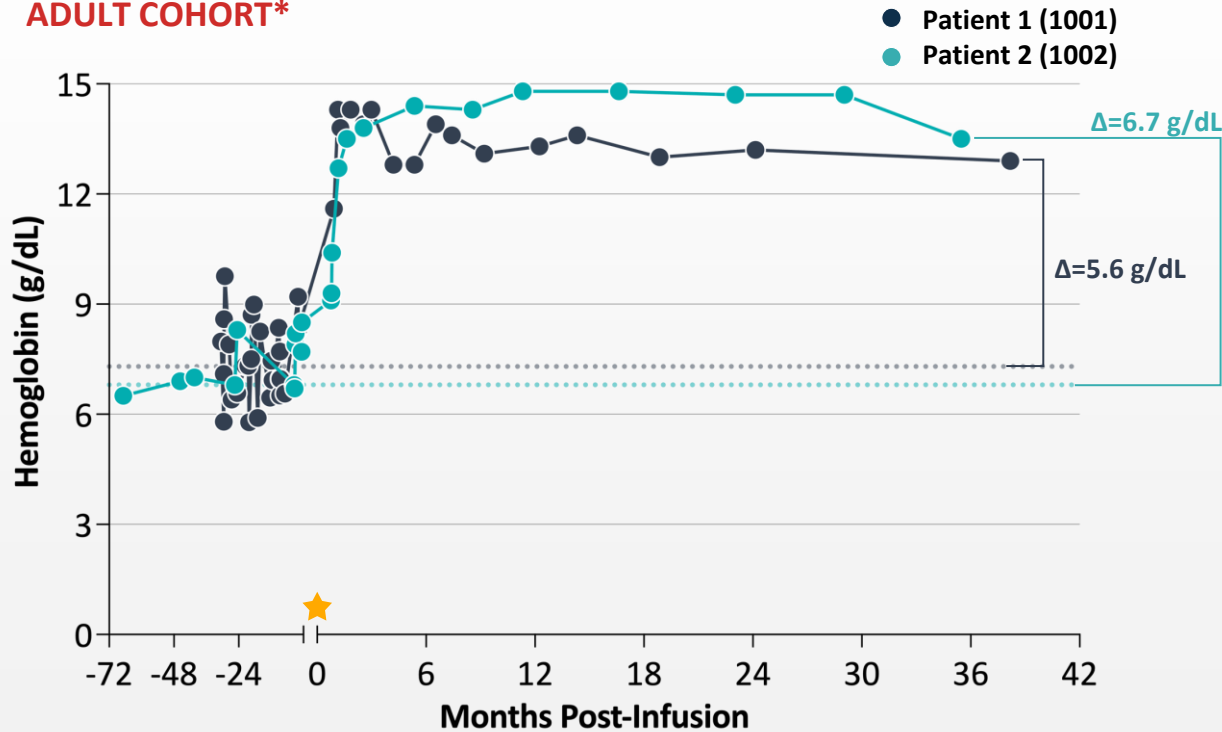
1. Rocket Pharmaceuticals data on file; 2. Tanaka K, et al. Pyruvate kinase (PK) deficiency hereditary nonspherocytic hemolytic anemia. *Blood*. 1962;19(3):267-295; 3. Zanella A, et al. Iron status in red cell pyruvate kinase deficiency: study of Italian cases. *British Journal of Haematology*. 1993;83(3):485-490; Zanella A, et al. Molecular characterization of the PK-LR gene in sixteen pyruvate kinase-deficient patients. *Br J Haematol*. 2001;113(1):43-48; Marshall SR, et al. The dangers of iron overload in pyruvate kinase deficiency. *Br J Haematol*. 2003;120(6):1090-1091; 4. Zanella A, et al. E. Pyruvate kinase deficiency. *Haematologica*. 2007;92(6):721-723; Grace RF, et al. Erythrocyte pyruvate kinase deficiency: 2015 status report. *American J Hematol*. 2015;90(9):825-830; Canu G, et al. Red blood cell PK deficiency: an update of PK-LR gene mutation database. *Blood Cells, Molecules, and Diseases*. 2016;57:100-109.

Preliminary Phase 1 Efficacy Results: Adult and Pediatric Patients

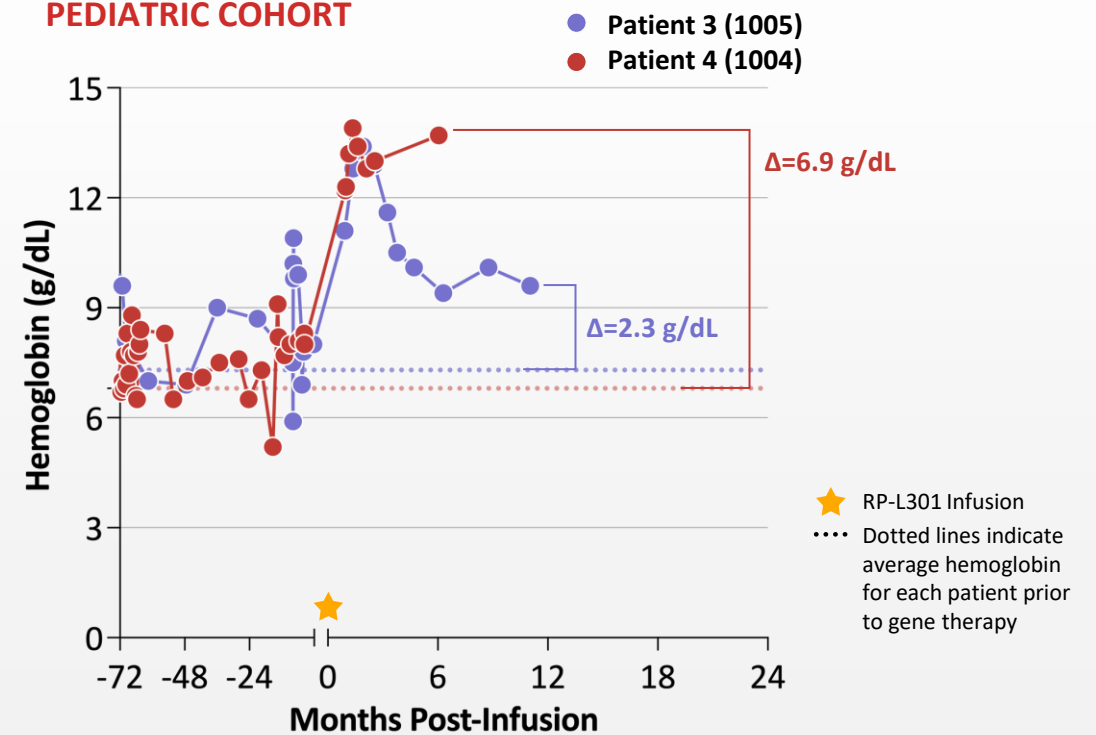


- Sustained & meaningful hemoglobin improvement from severe (<8 g/dL) baseline
- No RBC transfusions required following neutrophil engraftment
- Concurrent improvement across hemolysis biochemical markers

ADULT COHORT*



PEDIATRIC COHORT



★ RP-L301 Infusion
 Dotted lines indicate average hemoglobin for each patient prior to gene therapy

The average baseline Hb is determined by Hb values from 2y prior to enrollment to immediately prior to stem cell mobilization, excluding those impacted by RBC tx. Post-transfusion Hb values within 61d of a prior RBC tx were excluded unless the reported Hbb value was a pre-tx assessment for a subsequent RBC tx within 3 days of the prior RBC tx date. RBC, red blood cell. *Adult patient 2 underwent therapeutic phlebotomy 27 months through 36 months after gene therapy. Data cut-off: February 5, 2024; preliminary interim results are presented from the ongoing clinical study.

Development Plan



Alignment reached with FDA on pivotal Phase 2 trial design

PLAN FOR PHASE 2 AND LAUNCH

High level pivotal Phase 2 Trial Design

- Single-arm, 10 patient study
- Primary endpoint of $\geq 1.5\text{g/dl}$ increase in Hgb at 12 months post-infusion
- Supports accelerated approval

Well-delineated natural history in recent PKD NHS publications

REGULATORY DESIGNATIONS

Fast Track, RMAT, Orphan Drug (US/EU), PRIME, Rare Pediatric Disease (eligible for PRV)

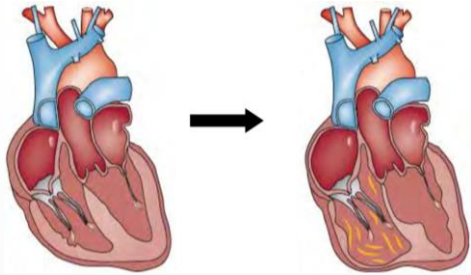
NEXT STEPS

- Phase 2 Pivotal Study Initiated

PKP2-Arrhythmogenic Cardiomyopathy (ACM)*:

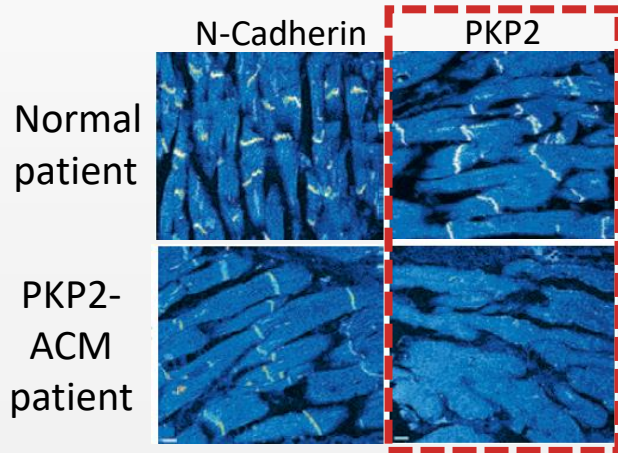
A high-risk disease with no curative options

Advanced ACM Heart with fibrofatty replacement in right ventricle



Electrical manifestations can precede structural abnormalities

ACM: Diminished Myocardial PKP2



Disease Etiology

- Autosomal dominant mutations in *PKP2* gene, which encodes for Plakophilin-2, a component of the desmosome localized to cardiac intercalated discs



Therapeutic Challenges

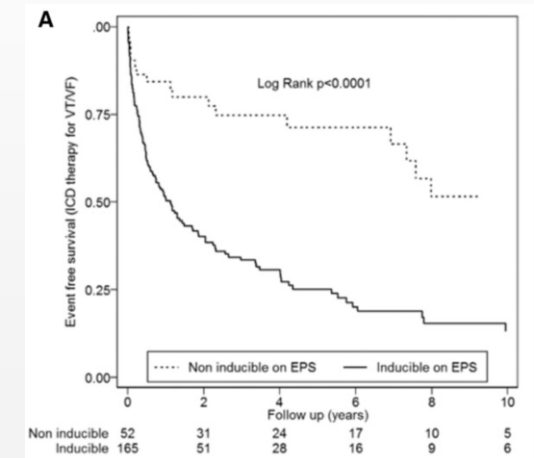
- Current standard of care includes beta-blockers, anti-arrhythmic agents, and ablation
- Available treatments do not modify disease progression; no curative therapeutic options



Clinical Manifestations

- Mean age at presentation: 35y (± 18)¹
- 5-10% annual risk of sustained ventricular arrhythmias (VA), with higher risk in patients who present with symptoms of disease (index patients)²⁻³
- In one study, >70% risk of VAs in index patients (median follow up, 7 years)⁴
- ICD placement in >80% of index patients⁵
- For patients with ICDs:
 - 45-75% will have ICD firing (shock) over 3-5 years
 - $\geq 50\%$ 2-year incidence of firing in subgroups:
 - male;
 - EPS-induced VT;
 - history of VT;
 - ≥ 3 ECG leads with TWI;
 - >1000 PVC/24h⁵⁻⁶

Kaplan-Meier Incidence of ICD Firing



Event free survival in ACM patients who underwent EP study prior to placement of an ICD

- ~70% of patients who were inducible on EP study had an ICD firing at 2 years

* This cardiomyopathy initially manifests in the right ventricular free wall, so the disease was termed arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/ARVC). However, since left dominant and biventricular forms have also been observed, this has led more recently to the use of the term "ACM". ECG, electrocardiogram; EPS, electrophysiologic study; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LV, left ventricle; PKP2; plakophilin 2; RV, right ventricular; RVEF, right ventricular ejection fraction; SD, standard deviation; SVA, sustained ventricular arrhythmia; TWI, T-wave inversion; VT, ventricular tachycardia.

Biopsy figure adapted from: Asimaki et al. NEJM, 2009; Table adapted from Dalal et al. Circulation 2006; 1. Bhonsale. EHJ 2015; 36: 847-55; 2. Towbin JA. Heart Rhythm 2019;16(11); 3. Cadrin-Tourigny J. Eur Heart J 2022;43; 4. Groeneweg. Circ Cardiovasc Genet 2015; 8: 437-46; 5. Calkins. Circ 2017; 136: 2068-82; 6. Orgeron. J Am Heart Assoc 2017: e006242.

PKP2-ACM Prevalence in the US and EU

ACM prevalence

1:1000 to 1:5000^{1,2}

PKP2 variants

32.9%

2,572 ACM patients assessed from 13 publications an aggregated mean of **32.9% had PKP2 mutations³**

ACM-PKP2 US & EU Prevalence

~50,000

Utilizing the conservative ACM prevalence (1:5000) and the 32.9% PKP2 mutation frequency in ACM

Proof of Concept in Translationally Relevant Animal Model

Completed RCKT Studies with *Cardiomyocyte-specific PKP2 Knockout Mouse Model of ACM*

- Initial POC evaluated 4 AAV Vectors: Cardiac Functional & Structural Analyses
- Dose-related effects evaluated with 2 AAV vectors: Cardiac Functional & Structural Analyses
- Evaluated Survival, Functional, and Anatomic Benefit in ‘Arrest Progression’ Models
 - Including delivery of AAV +7 or +14 Days after induction of PKP2 knockout and subsequent disease onset

Analyses Include:

- Survival
- Echocardiography and ECG
- PKP2 expression (IF and WB)
- Cardiac pathology & fibrosis
- Vector DNA, transgene mRNA
- General safety including pathology

Completed sponsored research

Academic Partner:

NYU Grossman School
of Medicine

Mario Delmar, MD, PhD

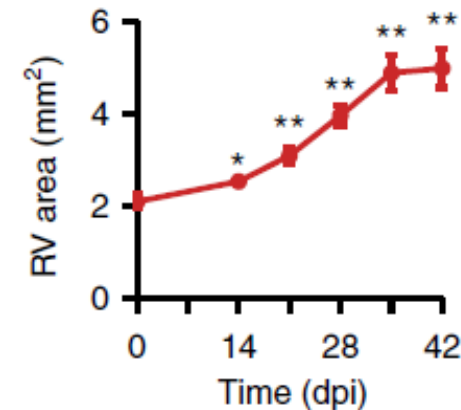
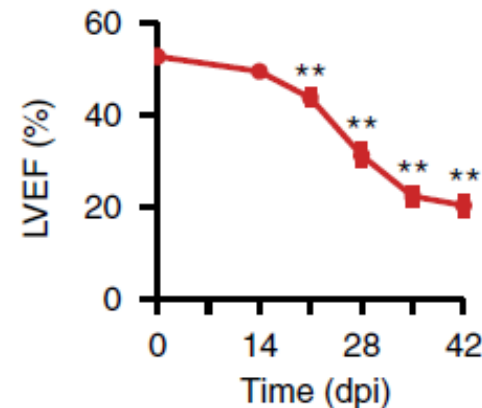
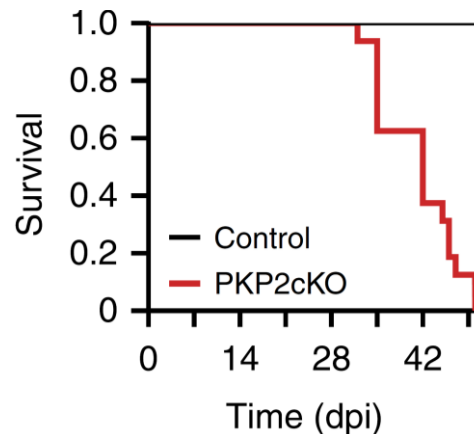
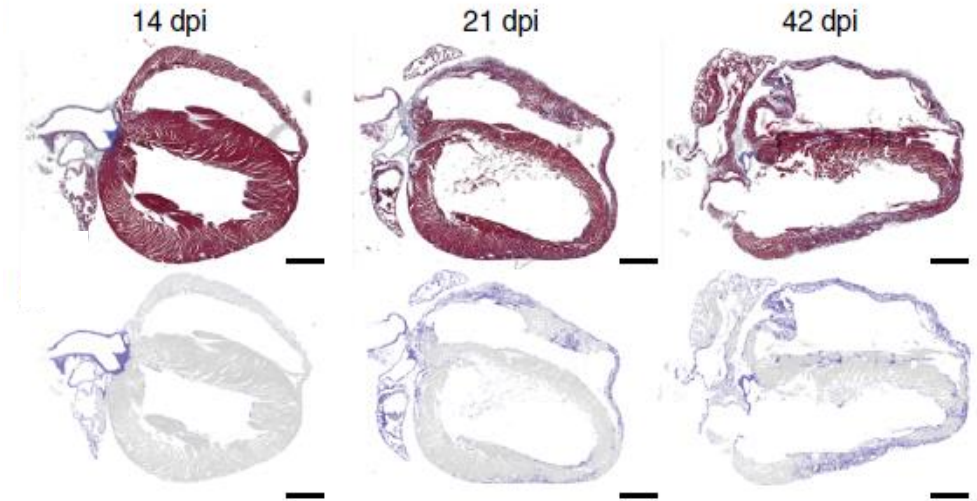
Patricia and Robert Martinsen Professor of Cardiology,
Department of Medicine; Division of Cardiology,
NYU Grossman School of Medicine

Marina Cerrone, MD

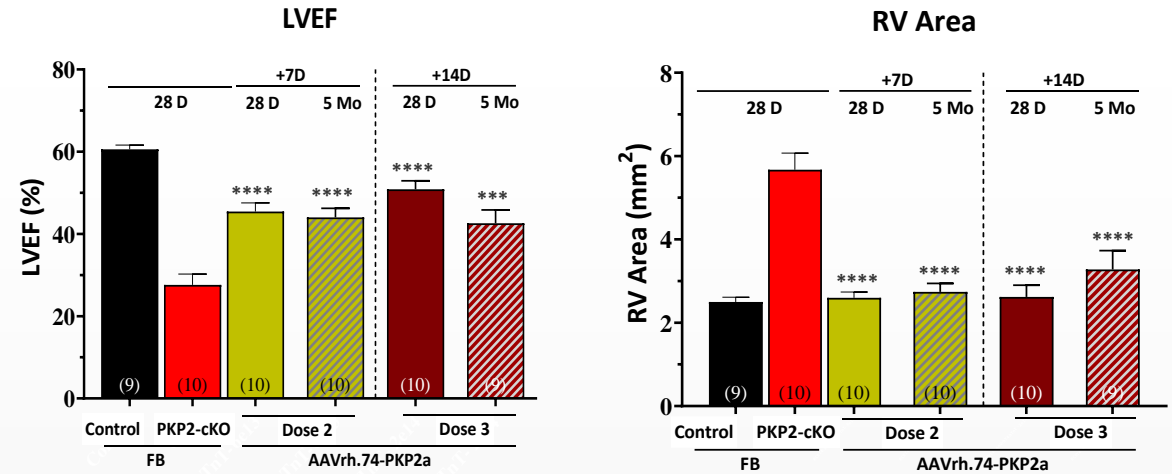
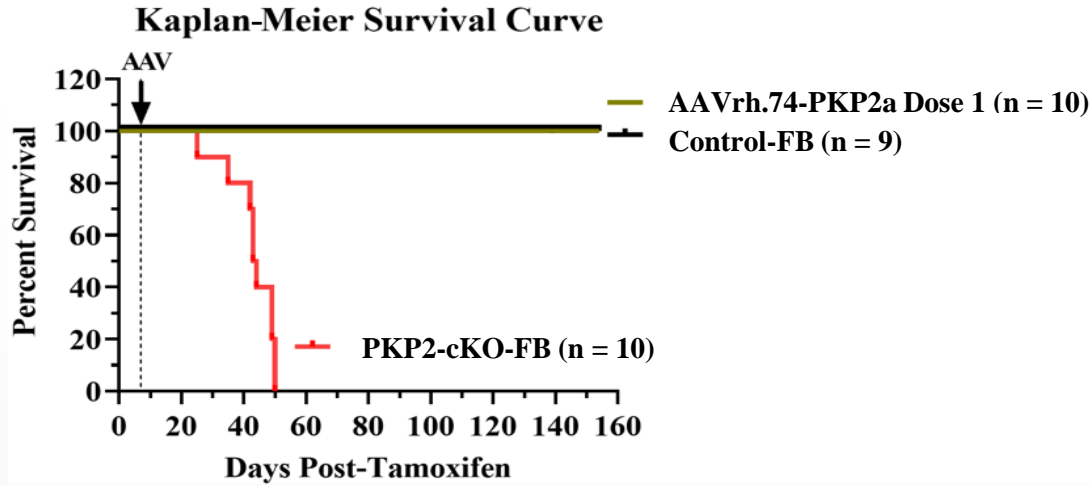
Research Associate Professor,
Co-Director, Inherited Arrhythmia Clinic,
Department of Medicine; Division of Cardiology,
NYU Grossman School of Medicine

Tamoxifen-induced ACM in the PKP2-cKO Mouse Model

- The PKP2-cKO mouse model recapitulates ACM following induction of PKP2 KO by tamoxifen injection¹
- Progression of cardiomyopathy evidenced by Masson's trichrome staining of heart sections in PKP2-cKO mice from 14 to 42 days post-TAM (dpi)
- 100% mortality by day ~50 following TAM injection
- Left ventricular ejection fraction diminishes significantly across time
- Right ventricular enlargement occurs across time
- Premature Ventricular Contractions are a clinical hallmark of ACM and emerge in the animal model because of PKP2 loss

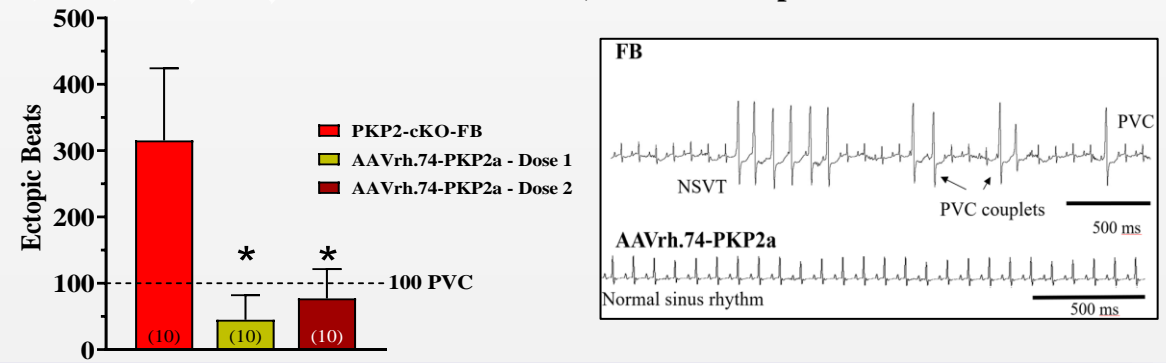


Increased Survival & Preserved Cardiac Function in the PKP2-cKO Model



- AAVrh.74-PKP2 delivered **7 days post-TAM**:
 - **100% survival to 5 months**, compared to 100% mortality by day ~50 in PKP2-cKO control animals
 - **Preserved Ejection Fraction and Right Ventricular Area** at 28 Days, sustained to 5 months
- AAVrh.74-PKP2 delivered **14 days post-TAM**:
 - Mitigated isoproterenol-induced PVCs and arrhythmia, disease-related characteristics of ACM
 - Robust benefit on survival, cardiac function & structure to 5 months¹

ISO-Induced Arrhythmia AAV+14D Post-TAM; ECG at 21D post-TAM



*p < 0.05 vs PKP2-cKO FB
ISO = isoproterenol; TAM = tamoxifen; ECG = Electrocardiography

¹Data not illustrated in Figures

Optimal Gene Therapy for PKP2-ACM Expected to be First-and Best-In-Class

cDNA/isoform:

- **PKP2a**: full wild type coding sequence of therapeutic gene, protein loss drives ACM

AAV Serotype:

- **AAV.rh74** serotype associated with favorable safety profile in DMD/LGMD2E¹⁻³; potential for safe administration at optimal doses for adult ACM patients

Cardiac-Specific Promoter:

- Effectively drives expression of therapeutic transgene in cardiomyocytes; minimizes off-target effects

Route of Administration:

- **IV** Pharmacology studies demonstrate efficient cardiac transduction with IV administration

Robust Proof of Concept in Disease Relevant Animal Model:

- **NYU Cardiac-specific cKO-PKP2 mouse** (biologically relevant translational model)

Clinical Development Plan



Phase 1 Dose Escalation Study

Completed or Ongoing Activities

- ✓ Phase 1 Study Initiated
- ✓ Enrollment complete in low-dose cohort
- ✓ Orphan Disease Designation
- ✓ GMP drug product manufacturing completed
- ✓ Pharmacology and GLP toxicology studies
- ✓ Potency assay
- ✓ Clinical protocol developed, vetted by Scientific Advisory Board and informed by patient insights
- ✓ Launching multi-center, clinical trial

High Level Phase 1 Trial Design

- Study design:
 - FIH, multi-center, dose escalation study to assess safety and preliminary efficacy
 - Starting dose of 8×10^{13} GC/kg
 - Target population: Adult PKP2-ACM patients with ICDs and high risk for arrhythmias
- Primary endpoint:
 - Safety events
- Secondary and exploratory endpoints:
 - PKP2 tissue protein expression
 - Clinical markers of life-threatening ventricular arrhythmias
 - Cardiac biomarkers

Natural History

- Natural history studies are planned to provide context for the Phase 1 trial and additional information on the progression of PKP2-ACM

BAG3 Regulates Critical Functions in Cardiomyocytes

Cardiac contractility

Enhances contractility by linking the β -adrenergic receptor and L-type Ca^{2+} channel

Structural support

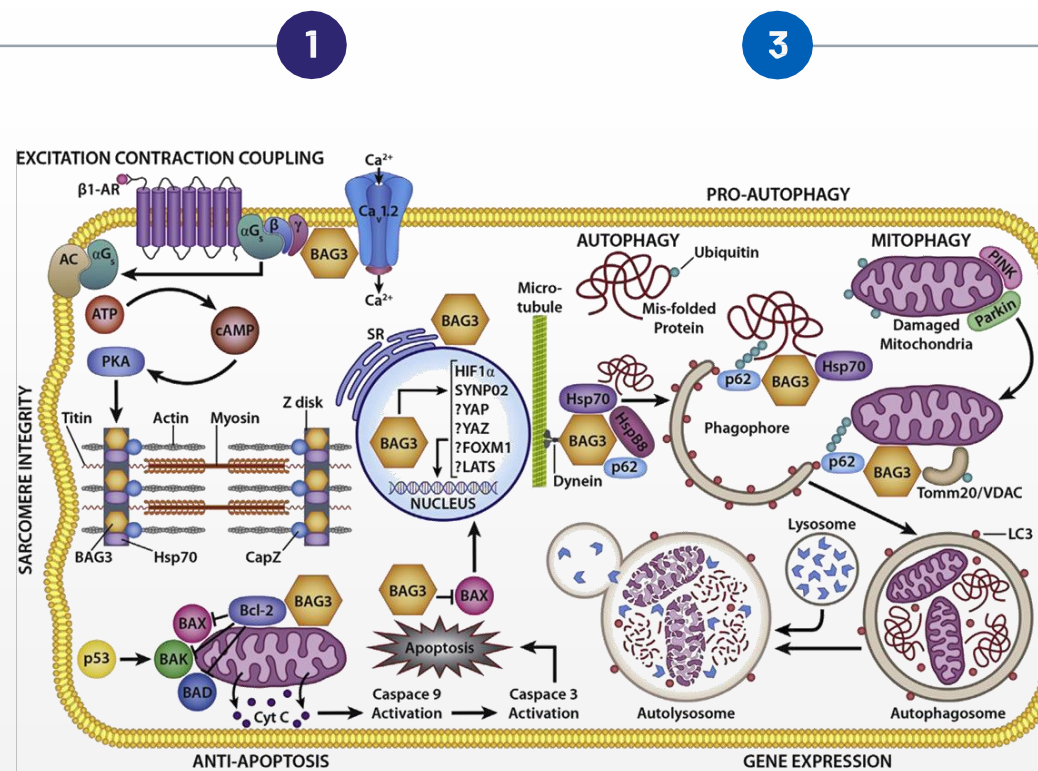
Provides support for the sarcomere by linking actin myofibrils with the Z-disc

Protein quality control

Facilitates autophagy as a co-chaperone with heat shock proteins, recycling misfolded proteins

Anti-apoptosis

Inhibits apoptosis (programmed cell death) through binding of BCL2



We believe that a gene therapy approach is best positioned to restore the broad biological functions of BAG3 in the heart

BAG3-DCM Opportunity and Next Steps

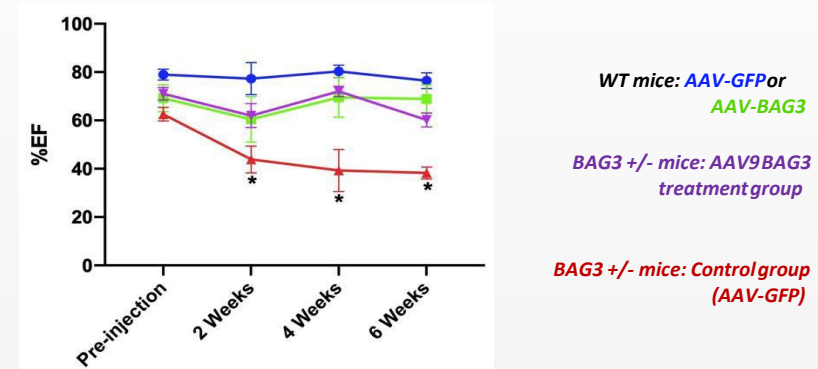
BAG3-DCM Represents a Significant Market with Unmet Need

- DCM is the most common form of cardiomyopathy
- 20% to 50% of DCM patients have familial DCM; up to 40% of whom have an identifiable genetic cause^{1,2}
- Scientific societies have endorsed clinical genetic testing for DCM patients and families^{3,4}
- Prevalence of BAG3 DCM in US is estimated to be as high as 30,000 patients^{5,6} and is expected to grow with increasing genetic testing and disease awareness

Initial Proof-of-Concept for AAV9-BAG3 Supports Further Development

- Initial proof of concept for AAV9-BAG3 demonstrated in BAG3-knockout mouse model

Ejection fraction in WT and BAG3 +/- mice treated at age 6 to 8 weeks with AAV9-GFP or AAV9-BAG3



- Evaluating optimal development pathway
- IND submission anticipated in the first half of 2025

Cranbury R&D and Manufacturing Facility Overview

- Total Lab Space: ~30,000 sq. ft. for process development, analytical development, MS&T and QC
- Manufacturing capability from small-scale to toxicology-scale material
- Streamlined tech transfer timeline for pipeline assets from plasmid selection to IND in <15 months
- Manufacturing expansion to add media and buffer production capability
- Incorporating fully automated in-house vial filler suite
- Anticipated 2X capacity increase

Enables rapid, robust and cost-efficient internal development capability for new and existing programs in addition to full-scale commercial manufacturing

~100,000 ft²
facility in Cranbury, NJ



Future Therapies: Wave 2 (AAV)



Current Clinical Pipeline

Focused R&D Strategy for Sustainable Innovation



First-, best- and/or only-in-class



On-target MOA; clear endpoints



Sizeable market to maximize patient impact

**3 therapeutic areas
(CV, hemetology and undisclosed)**

We continue to build our pipeline based on our core R&D strategy, identifying the “most impactful” indications for the most efficient development path.

Expert Leadership With Proven Track Record



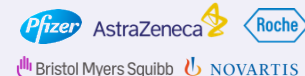
Gaurav Shah, M.D.

Chief Executive Officer
Spearheaded Kymriah (CART-19) development at Novartis towards approval



Kinnari Patel, Pharm.D., MBA

President, Head of R&D and Chief Operating Officer
Led Opdivo and six rare disease indication approvals



Jonathan Schwartz, M.D.

Chief Medical & Gene Therapy Officer
Led multiple biologics approvals



Aaron Ondrey

Chief Financial Officer
20+ years of experience in commercial finance, strategic planning, and M&A across multiple therapeutic areas



Mayo Pujols

Chief Technical Officer
~30 years technical operations and GMP manufacturing expertise



Mark White, MB.ChB.

General Manager, Commercial Affairs
Seasoned drug developer with 25+ years of industry experience



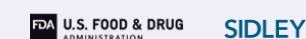
Martin Wilson, J.D.

General Counsel & Chief Corporate Officer
~20 years legal, compliance and executive experience and accomplishment in life sciences



Gayatri R. Rao, M.D., J.D.

Chief Regulatory Officer & SVP, Clinical Safety
7-year former Director of FDA's Office of Orphan Products Development



Raj Prabhakar, MBA

Chief Business Officer
~20 years cell, gene and biotech business development



Carlos Martin, BA, MBA

Chief Commercial Operations & Revenue Officer
15+ years global & local leadership, commercial strategy and new product launches



Isabel Carmona, J.D.

Chief People Officer
Seasoned leader in human resources, legal and compliance across life sciences, financial services and IT





THANK YOU!

