



SEEKING GENE THERAPY CURES



DISCLAIMER

Various statements in this presentation concerning Rocket's future expectations, plans and prospects, including without limitation, Rocket's expectations regarding its guidance for 2024 in light of COVID-19, the safety, effectiveness and timing of product candidates that Rocket may develop to treat Fanconi Anemia (FA), Leukocyte Adhesion Deficiency-I (LAD-I), Pyruvate Kinase Deficiency (PKD), Danon Disease (DD), PKP2-ACM (PKP2), BAG3-DCM (BAG3) and other diseases, and the safety, effectiveness and timing of related pre-clinical studies and clinical trials and related data readouts, 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 when clinical trial sites will resume normal business operations, 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, 2022, filed February 28, 2023 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.

Vision: Seeking Gene Therapy Cures

Values

Trust

Curiosity

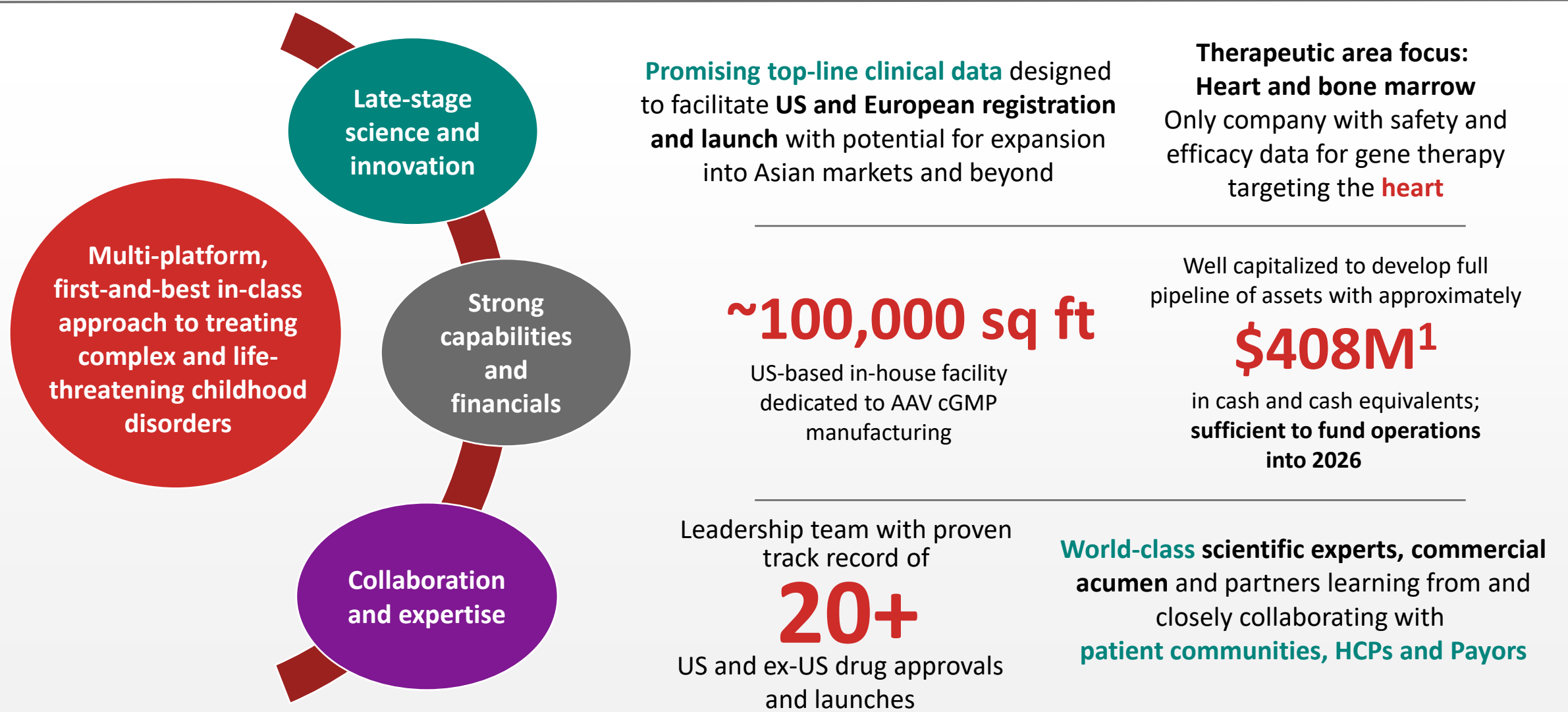
Elevate

Generosity

Mission

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

A Fully Integrated Commercial Stage Gene Therapy Company



Strong Science, Carefully-selected Assets and Smart Execution

6 Disclosed programs with compelling clinical evidence and significant commercial potential

Criteria used to select programs



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

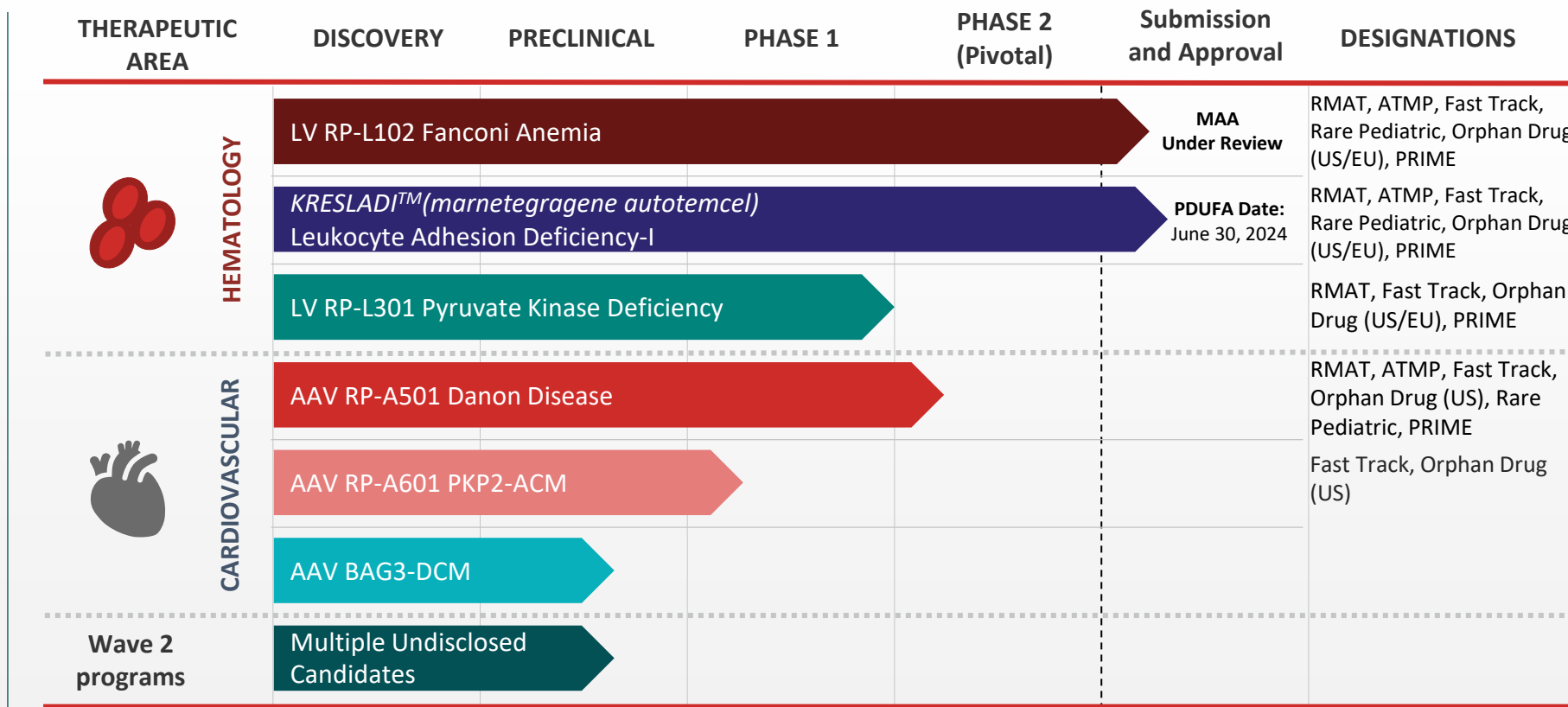


On-target MOA; clear endpoints



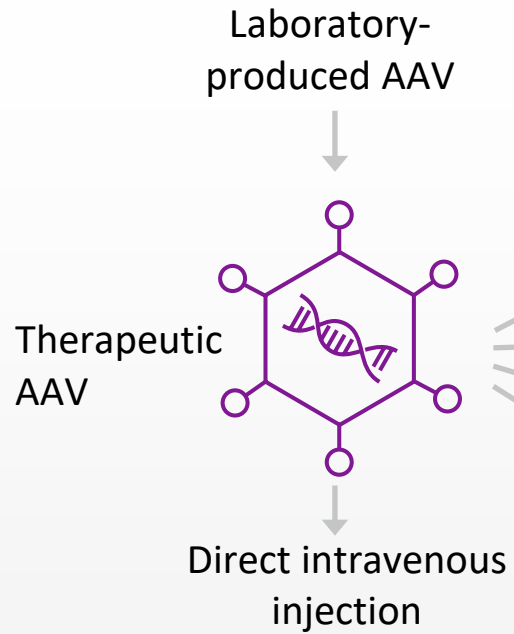
Sizeable market to maximize patient impact

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



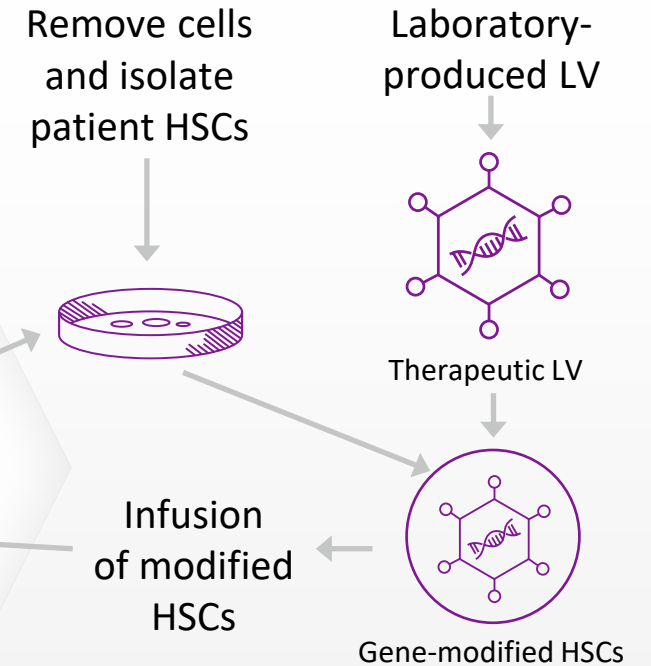
Rocket Offers Multi-platform Gene Therapy Expertise

IN VIVO platform



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

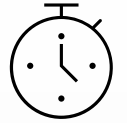
EX VIVO platform



- 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



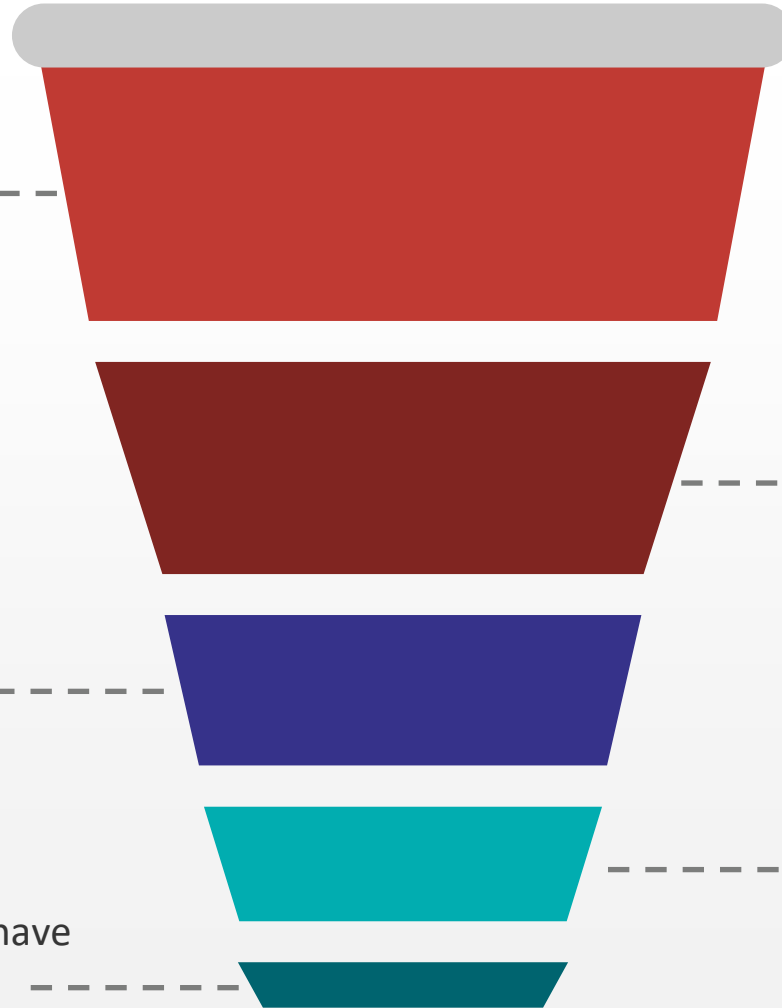
400 million
people globally are
affected by a rare disease¹



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

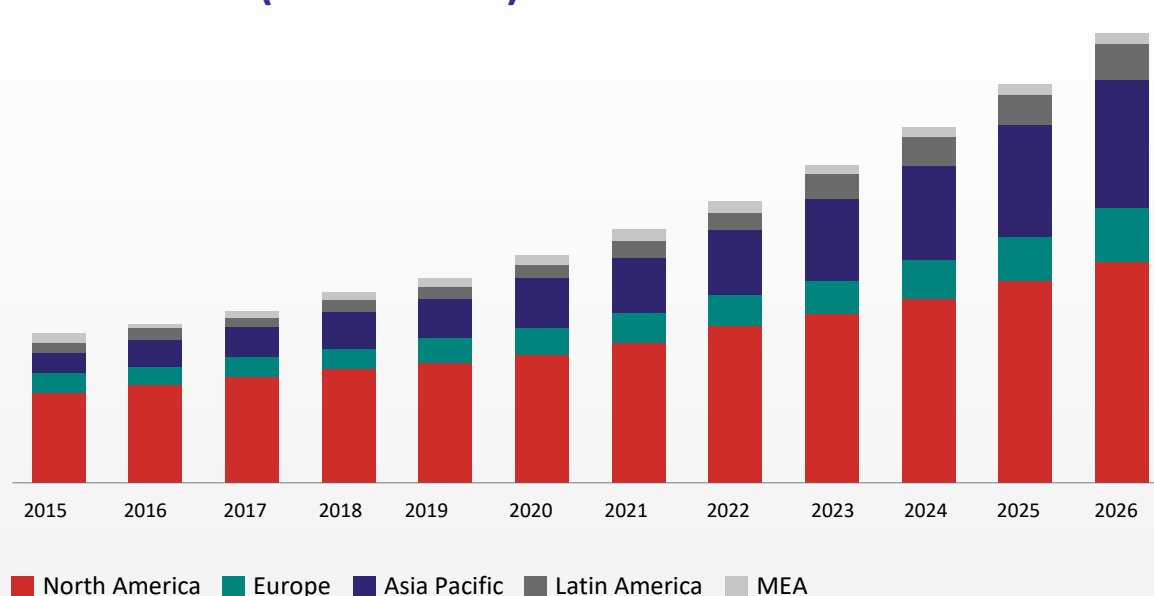


3 of 10 children
with a rare disease die
before their fifth
birthday¹



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



- 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

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

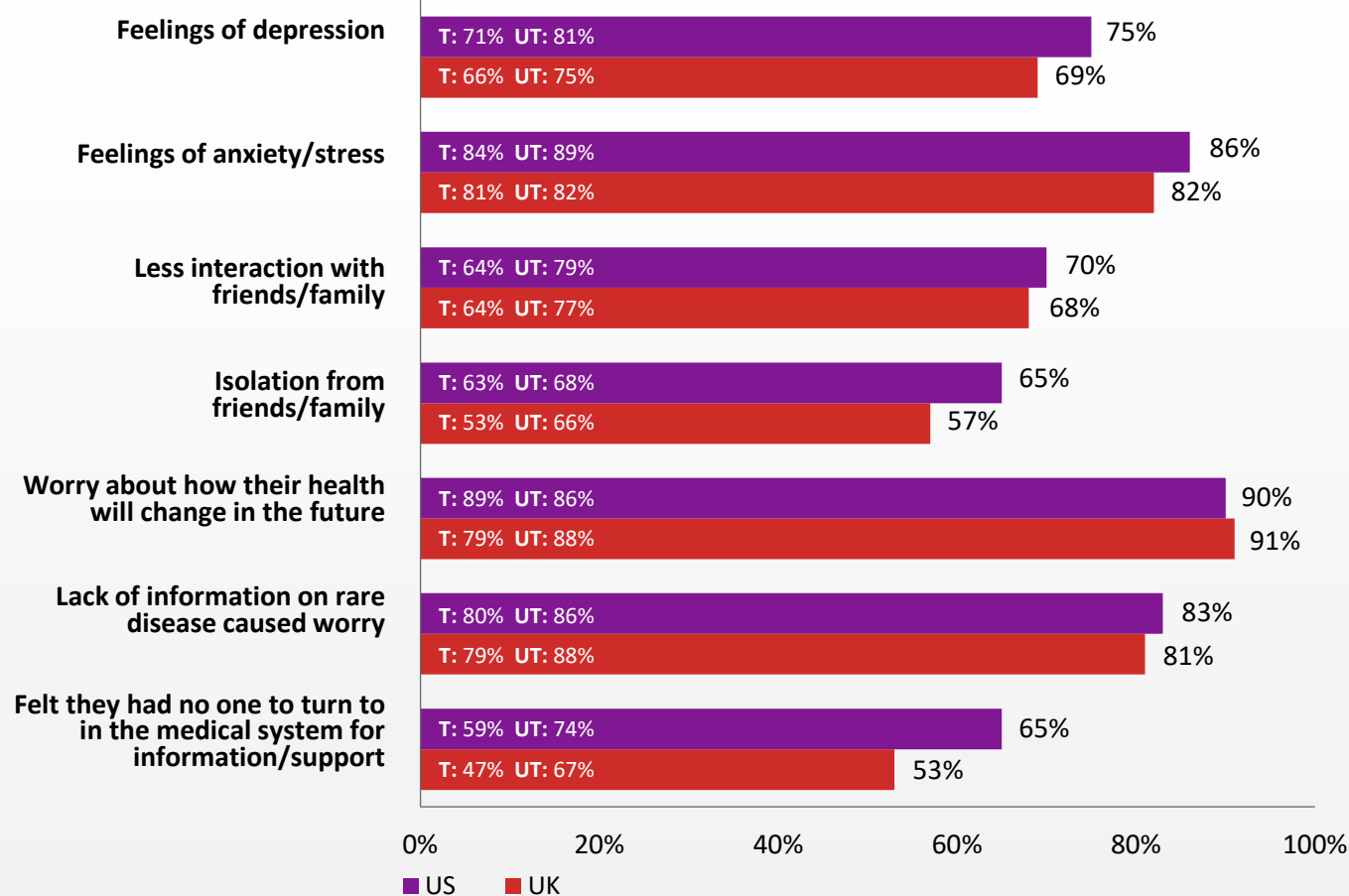


Patients with rare diseases or their caregivers are often compelled to leave the workforce²



Cost of bone marrow and heart transplants & maintenance is high

Emotional impact⁴



*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. Data on file. Rocket Pharmaceuticals. 2022. 4. Global Genes. Accessed April 2022. <https://globalgenes.org/wp-content/uploads/2013/04/ShireReport-1.pdf>

Danon Disease (DD): 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 (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

Market Opportunity – US and EU

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

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 (17.4 aai)	36	1	-75% (M18)	-36%	311 → 212	85 → 57	25 → 23	II → II	44 → 49
	1002 (20.3 aai)	36	3	-79%	-76%	989 → 511	260 → 129	64 → 38	II → II	64 → 81
	1005 (18.3 aai)	30	2 (M9)	-57% (M9)	-64% (M9)	438 → 375	98 → 76	33 → 24	II → I	77 → 85 (M24)
High dose adult/adolescent	1006 (21.1 aai)	24	1	-47%	-70%	410 → 300	90 → 63	22 → 18	II → I	79 → 82
Low dose pediatric	1008 (12.3 aai)	12	1	-86%	-83%	605 → 447	140 → 96	42 → 39	II → I	50 → 82
	1009 (11.7 aai)	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

Latest Phase 1 Pediatric Data Shows Sustained Improvements in Biomarkers, Symptoms, and Function

Subject ID: A501-008-1008

Baseline Characteristics

AGE AT INFUSION	MAX LV WALL THICKNESS
12.3 years	41.9 mm, z-score +32
ICD yes ¹	6MWT
WPW yes	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



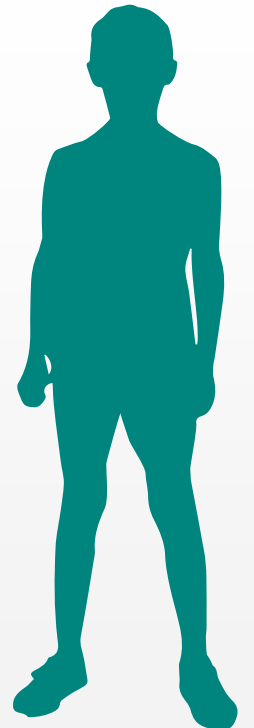
Subject ID: A501-008-1009

Baseline Characteristics

AGE AT INFUSION	MAX LV WALL THICKNESS
11.7 years	19.8 mm, z-score +12
ICD no	6MWT
WPW no	553 meters

12 months

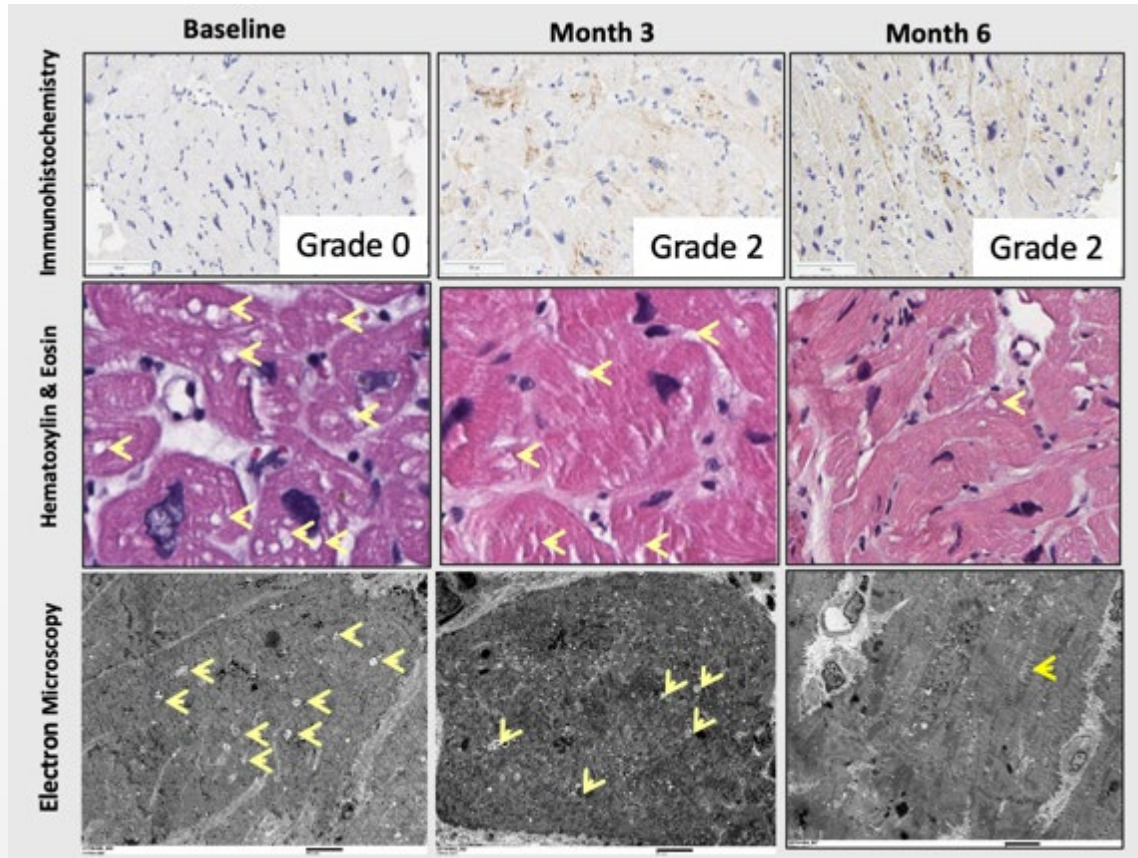
Variable	Baseline ²	Most Recent Follow-up
LAMP2 protein ³	0	1 (M6)
Troponin-I (ng/mL)	0.67	0.08 (-88%)
BNP (pg/mL)	297	163 (-45%)
NYHA Class	II	I
LV Mass Index	83	60 (-28%) ⁴



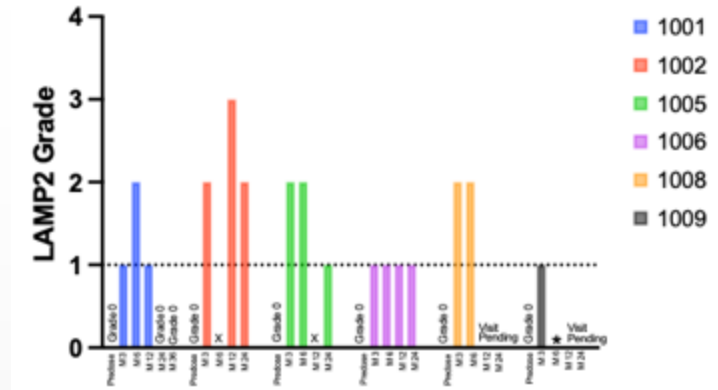
RP-A501 Increases LAMP2 Protein and Decreases Vacuolization

Enhanced autophagy leads to improved myocardial ultrastructure and clinical phenotype

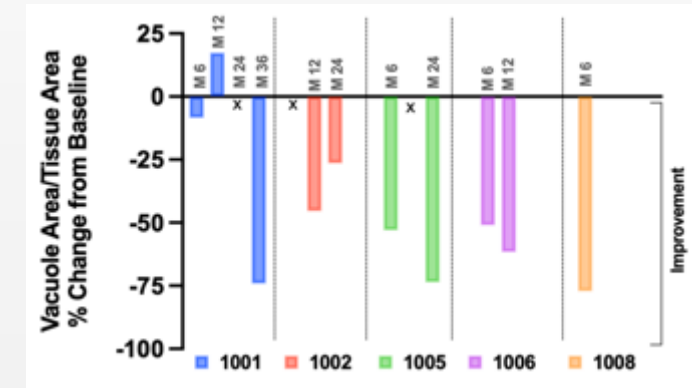
Endomyocardial Biopsy Images
(Subject 1008, RP-A501 Phase 1 Study)



Myocardial LAMP2 Protein Expression

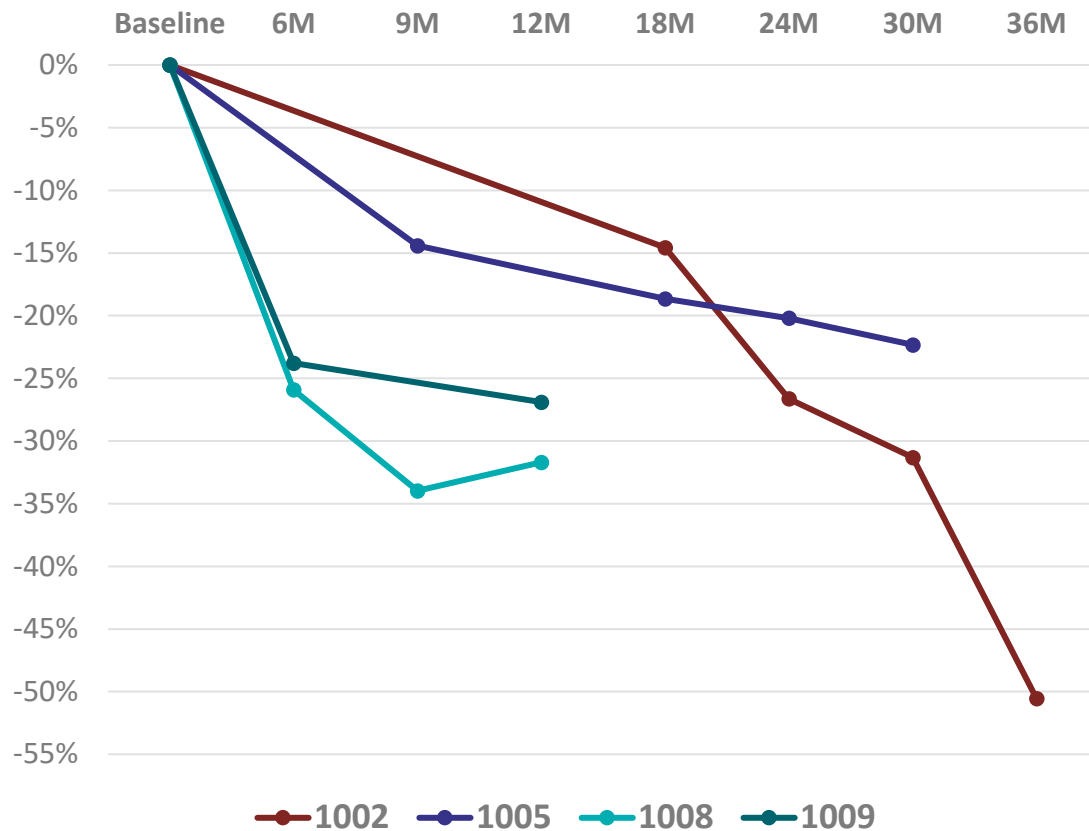


Vacuolar Area of Endomyocardial Tissue

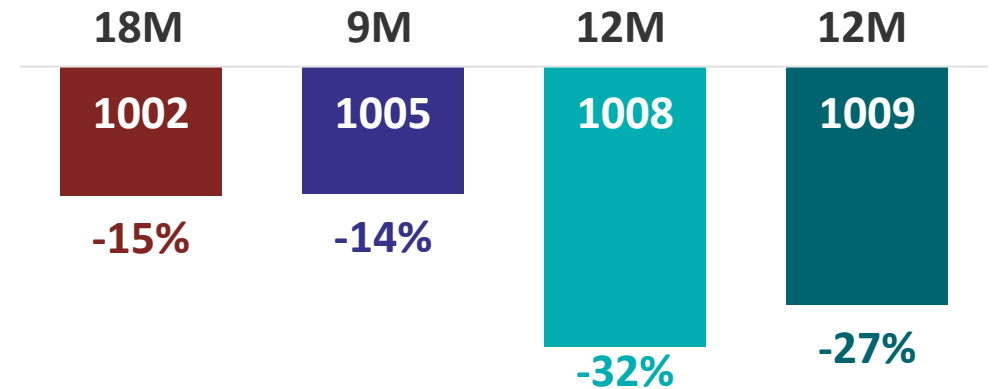


LV Mass Index in RP-A501 Phase 1 Study

RP-A501 Phase 1 Low-Dose Cohort: LV Mass Index % Change from Baseline¹



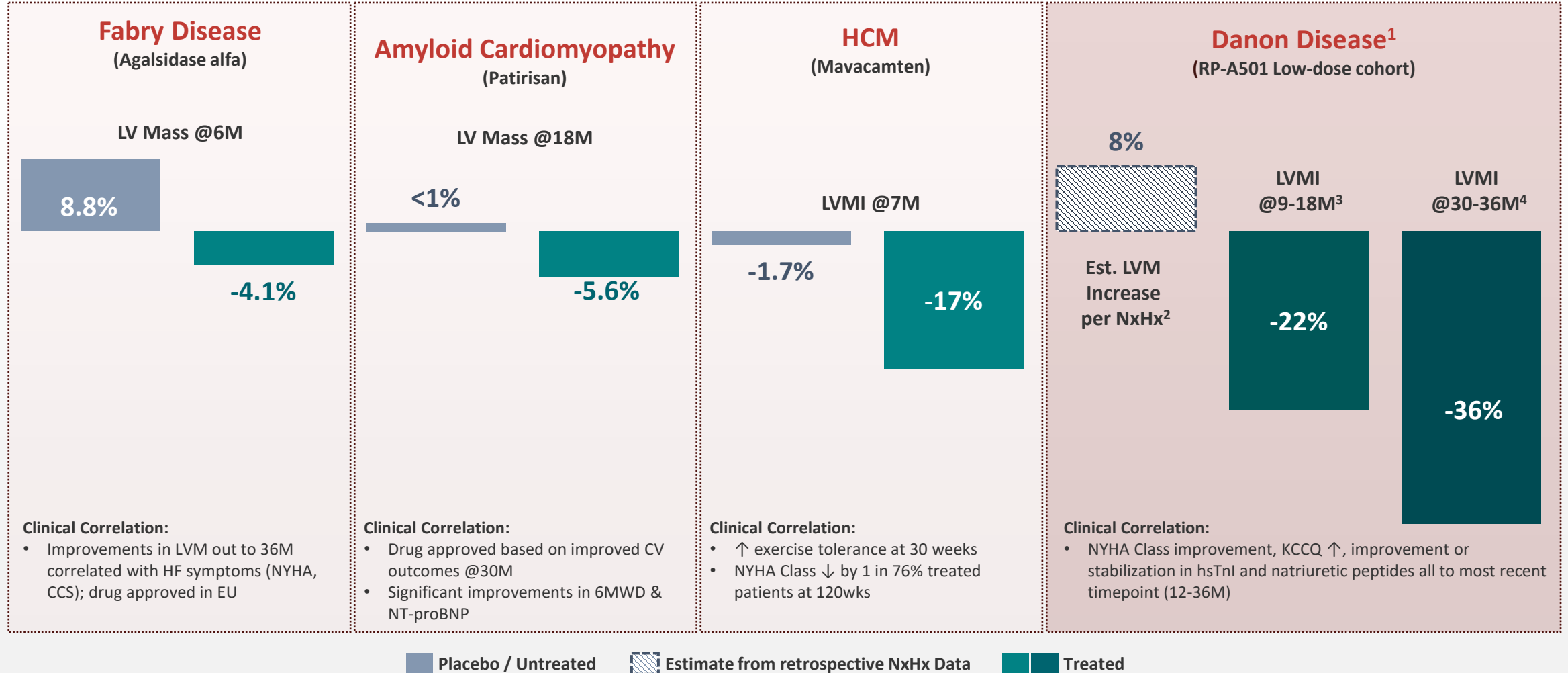
RP-A501 Phase 1 Study: LV Mass Index % CFB at ~12M (9M or 18M where 12M not available)²



- **>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 12M² with further decreases out to 30-36M of 22% to 51%**

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

LV hypertrophy decreases greater than/comparable to other approved therapies



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

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. -Pt 1005

Prior to therapy, he was afraid of dying and wanted a chance at life.....After gene therapy, we see him smile more now, he bought 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 -Pt 1006

He went to overnight summer camp on his own for the first time and is no longer out of breath walking up stairs. -Pt 1008

He walked a 10K with his father following treatment. He is exercise training twice a week for an hour. -Pt 1009

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

Adolescent/Adult Cohort ≥15y

RP-A501 Tx

(Additional pediatric dosing following Safety Run-in)

Primary Endpoint Assessment

~12m

END OF STUDY

60m

Pediatric (8-14y) Safety Run-in (n=2)

RP-A501 Tx

Peds pt #1 Peds pt #2

90d

← 1m →

← Safety observation →

- Dose: 6.7×10^{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 hsTnl

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

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 model¹
- Phase 1: LAMP2 expression associated with decreased vacuolar area, improved myofibrillar disarray, clinical improvement

Left Ventricular Mass

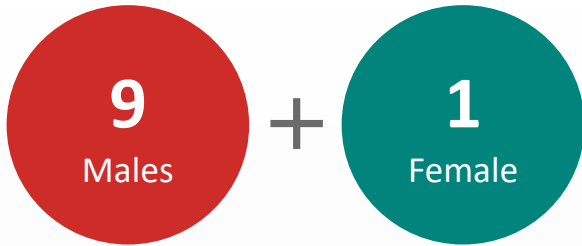
- Largest known hearts are Danon disease hearts
- Severity of the cardiomyopathy in Danon disease is the major prognostic factor²
- Retrospective natural history shows year-over-year increases in LV mass in Danon disease patients
- Phase 1: Consistent and significant reductions in LV mass as early as 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*

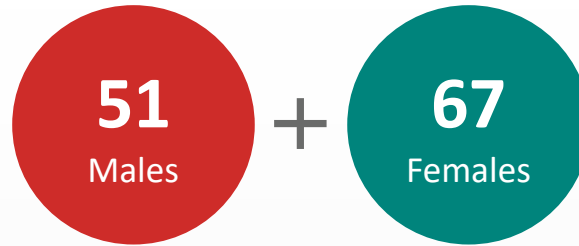
Natural History Studies

Prospective Natural History Study



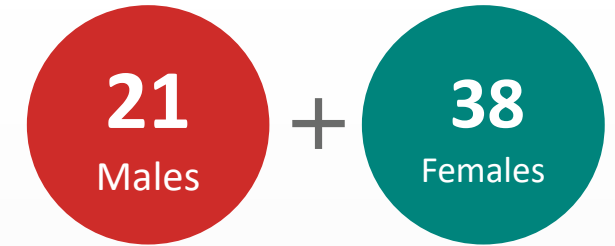
Initiated in 2019, study complete

US Retrospective Natural History



Initiated in 2006

EU Retrospective Natural History Study

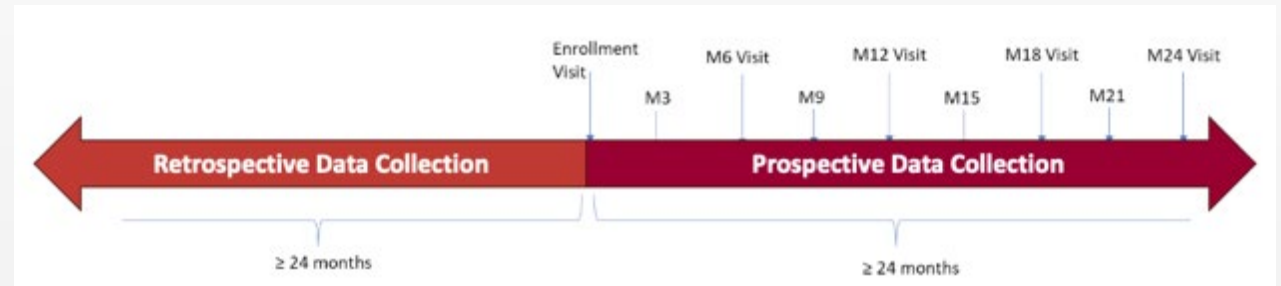


Enrollment complete; analysis in Q4 2023

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

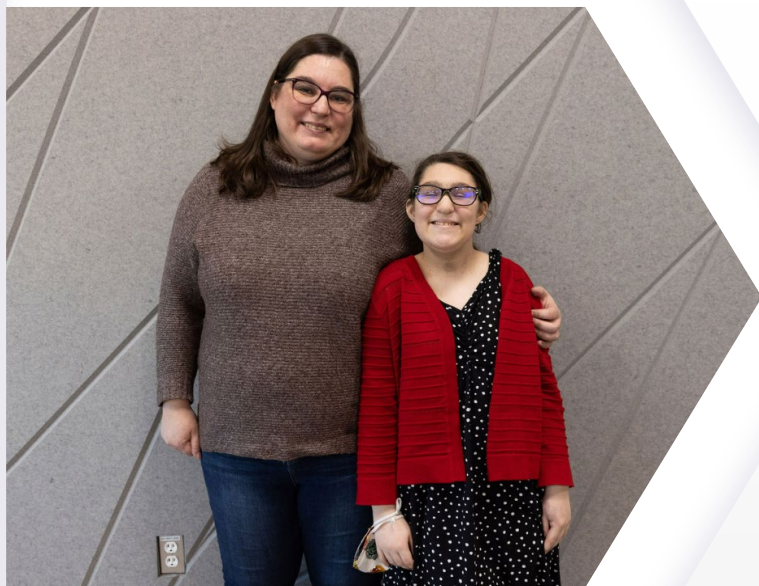


In-House Manufacturing to Support Danon Pivotal Study and Commercial Production

- **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 (FA-A)



Fanconi Anemia (A, C, and G)

Market Opportunity – 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 challenges

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 life
- Predisposition to hematologic malignancies and solid tumors

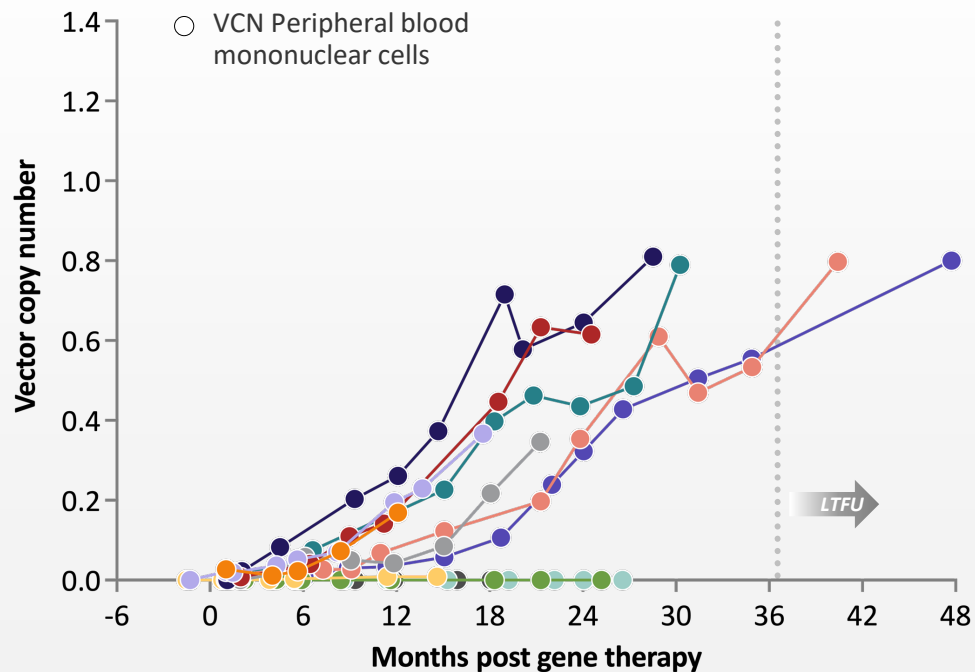
*Gene therapy approach: Selective advantage of corrected cells allows for **ex-vivo LV therapy without conditioning**; highly favorable benefit risk profile*

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

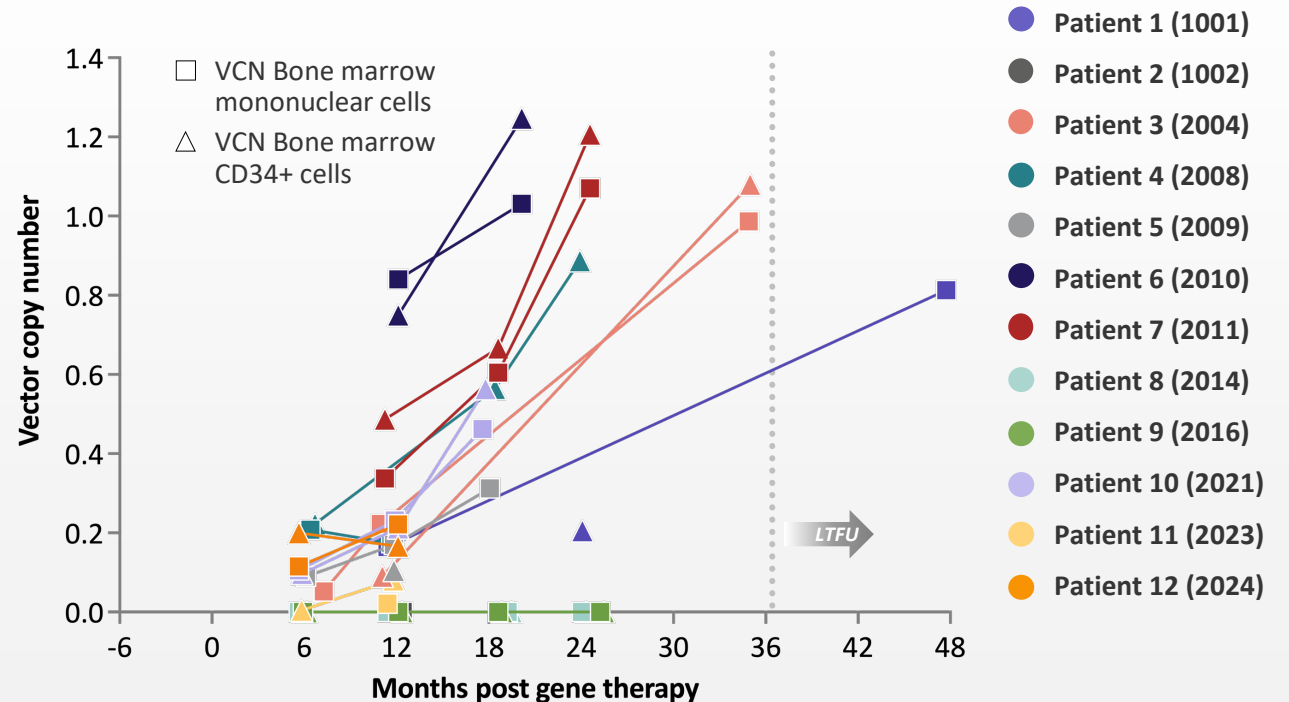


Progressive increases in PB and BM gene marking in 8 patients

PBMC VCN



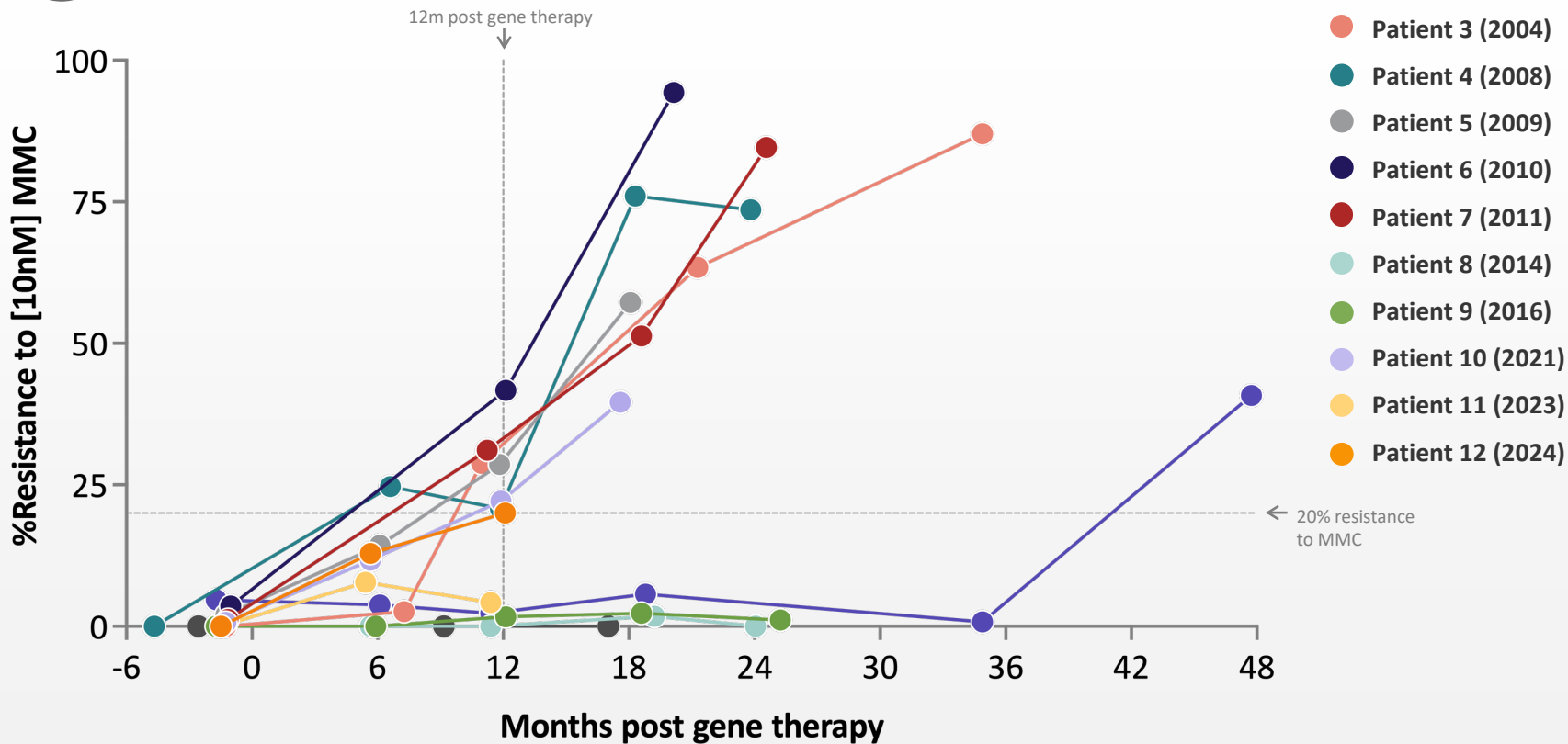
BM VCN



Increasing Phenotypic Correction (MMC-resistance) 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 CFC MMC resistance confirmed in 6 patients *



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

For 6 patients, increased BM CFC MMC resistance (40% to 94%) was observed 18 to 24 months post RP-L102 (confirmatory assessment pending for pt 2024)

BM, bone marrow; CFC, colony-forming cells; 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: April 17, 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

- Initial comprehensive efficacy in 7/12 evaluable patients (≥12-month follow-up)
- No cytotoxic conditioning, only 1 transient RP-L102 related SAE (Grade 2)

TOP-LINE DATA READOUT ACHIEVED

- Rejection of null hypothesis with minimum of 5 patients with increased MMC resistance >10% at 2 timepoints between 12 and 36 months

NEXT STEPS

- MAA submission accepted – under review
- Anticipated BLA submission in 1H 2024

Additional life-cycle management activities:

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

REGULATORY DESIGNATIONS:

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

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



Market Opportunity – 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

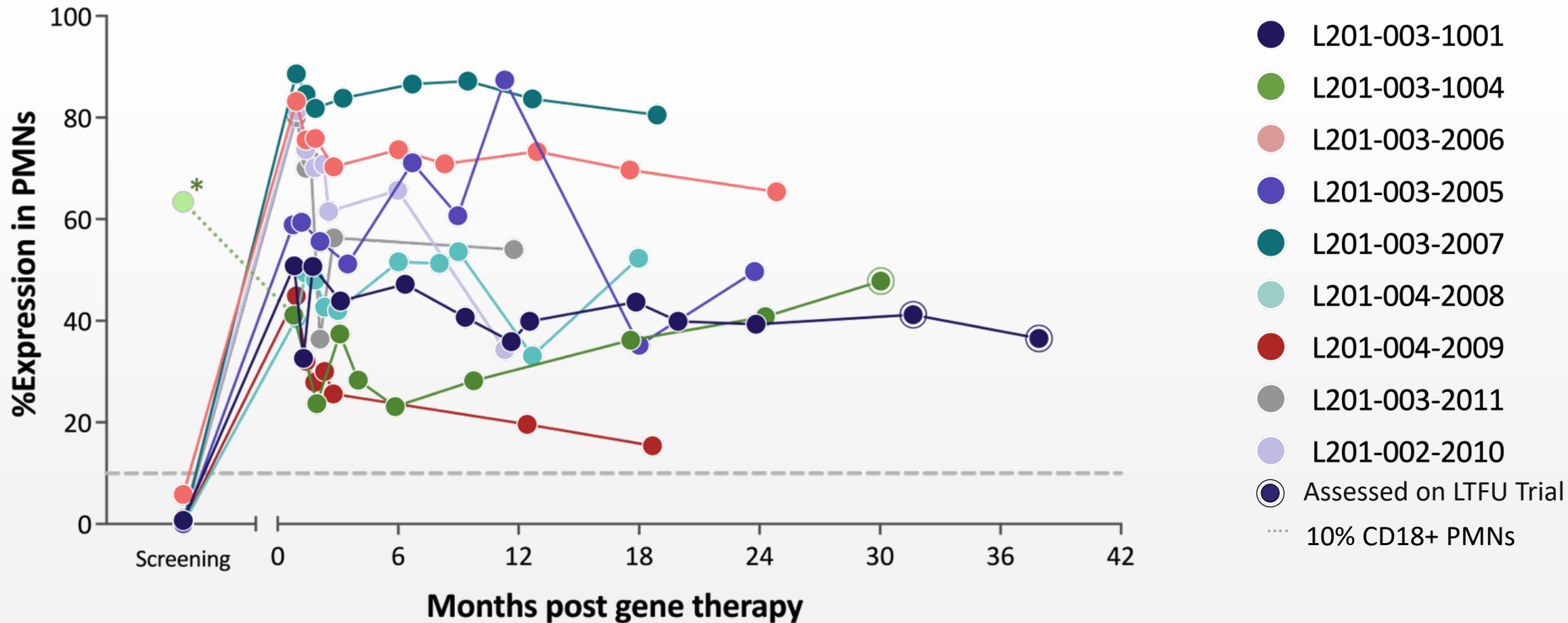
Patients suffer from recurrent infections; fatal in majority

- 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 (PMNs) in Pivotal Phase 1/2 Trial



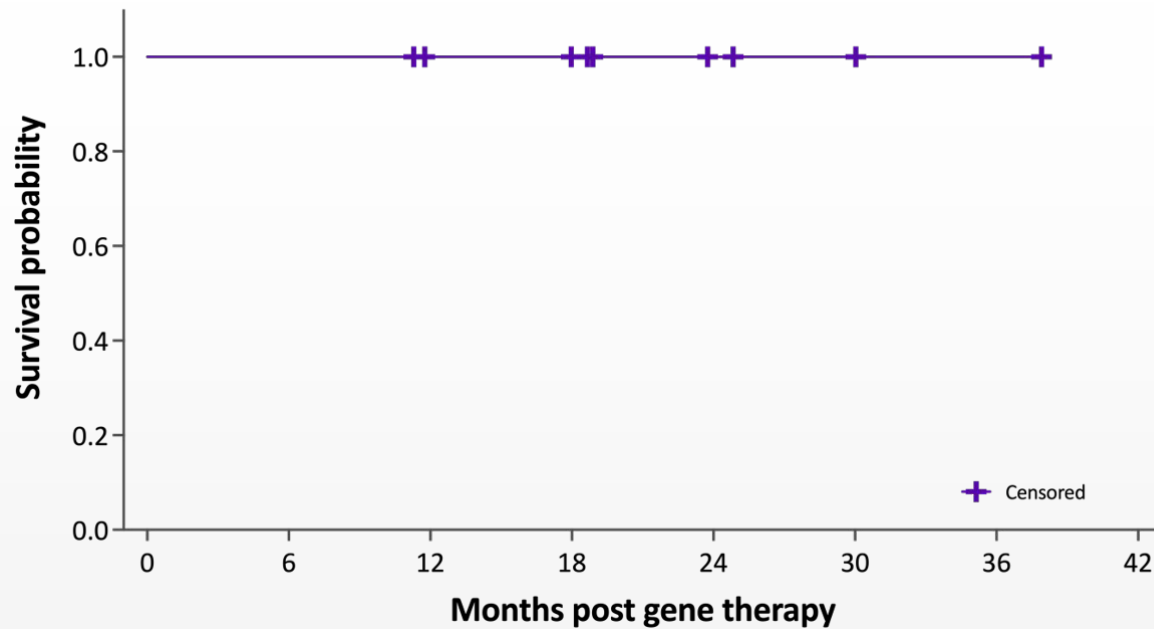
Sustained >10% PMN CD18 expression after 1 year of gene-corrected cell infusion across the entire cohort



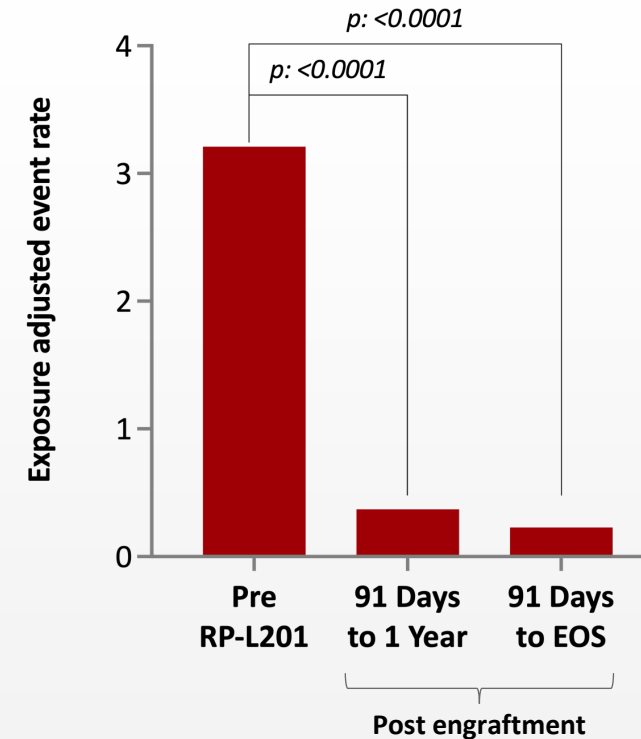
*Dim/weak CD18 expression reported at baseline for Subject L201-003-1004 in ~63% of cells in conjunction with <2% CD11a/CD11b expression, likely indicating abnormal/unstable protein. LAD-I, Leukocyte Adhesion Deficiency-I; PB, peripheral blood; PMN, polymorphonuclear neutrophil. Data on file. Rocket Pharmaceuticals. 2023. Data Cut-Off: November 2, 2022; Preliminary interim results are presented from the ongoing clinical study.

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

100% HSCT-free survival Kaplan–Meier estimate



Significant reduction in incidence of hospitalizations[^]



Survival without allogeneic HSCT*

Primary outcomes

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

All patients have been able to stop prophylactic antibiotics

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

- PDUFA Date: June 30, 2024

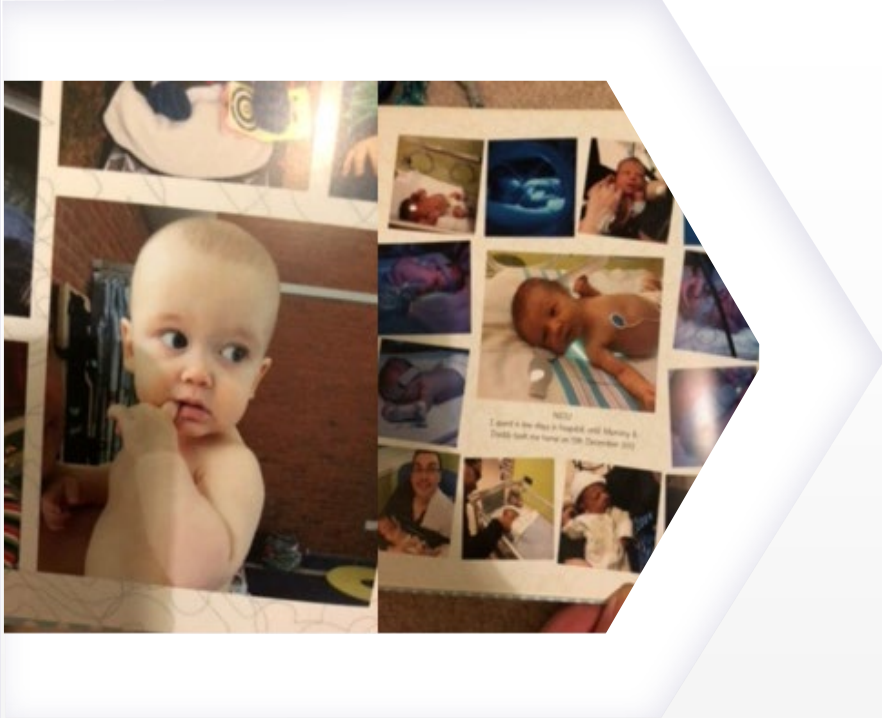
Life-cycle management

- Potential label expansion to include moderate LAD-I population

REGULATORY DESIGNATIONS:

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

RP-L301 for PKD: *PKLR* Gene Mutation



Disease etiology

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



Therapeutic challenges

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



Clinical manifestations

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

Market Opportunity – US and EU

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

Annual incidence of **75 to 125** individuals

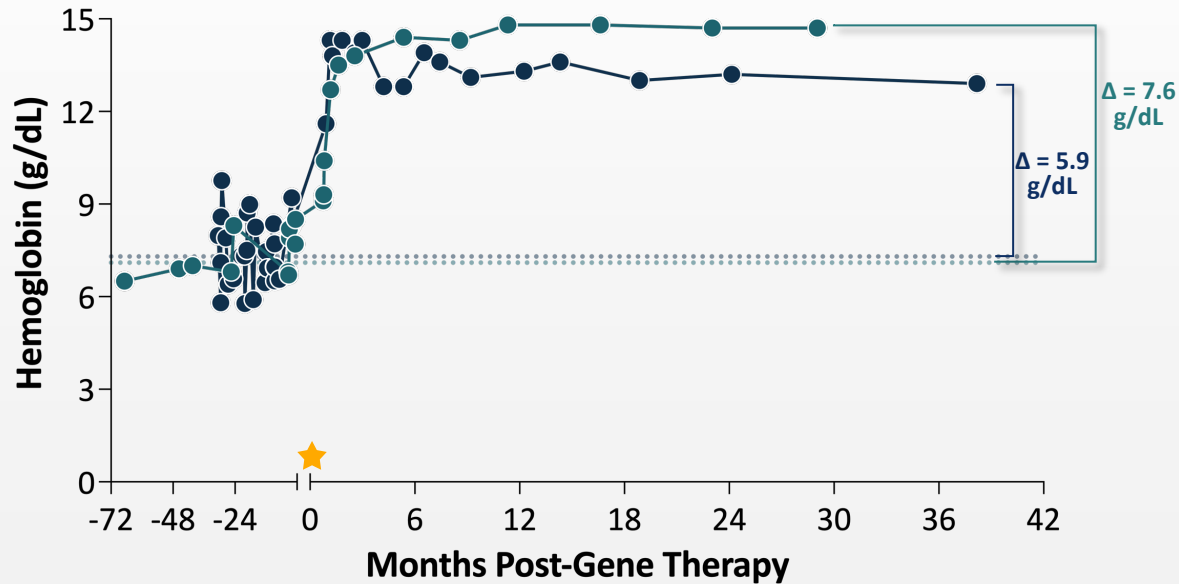
Preliminary Phase 1 Efficacy Results: Adult and Pediatric Patients



Sustained & meaningful hemoglobin improvements from severe (<8 g/dL) baselines
 No RBC transfusions required following neutrophil engraftment
 Comprehensive improvement across hemolysis markers (LDH, bilirubin); PB VCNs up to 2.0

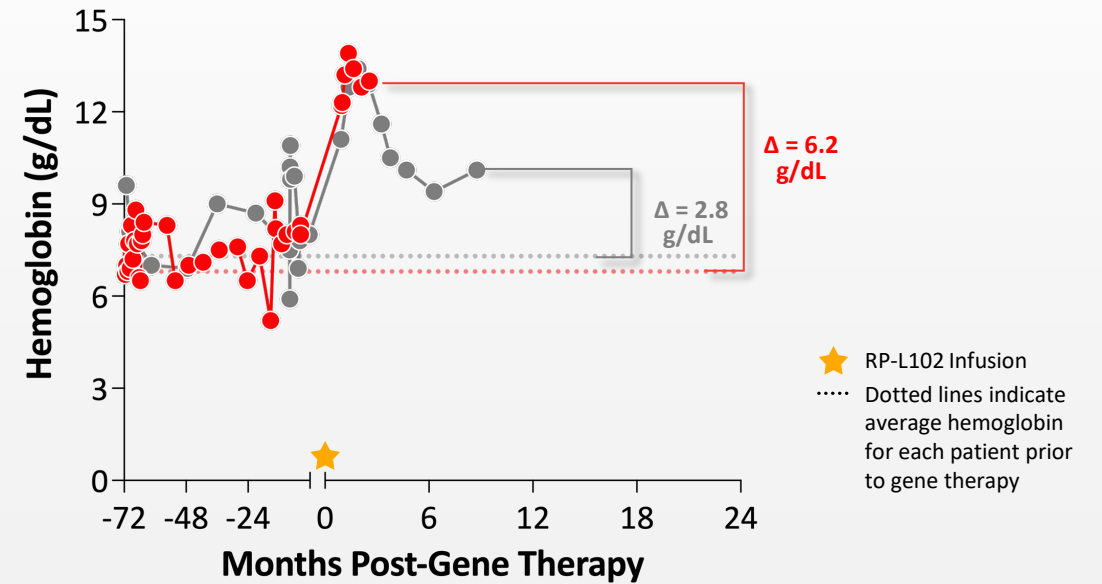
ADULT COHORT

● Patient 1001
 ● Patient 1002



PEDIATRIC COHORT

● Patient 1005
 ● Patient 1004



★ RP-L102 Infusion
 Dotted lines indicate average hemoglobin for each patient prior to gene therapy

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 ≥ 1.5 -point Hgb improvement at 12 months
- 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)

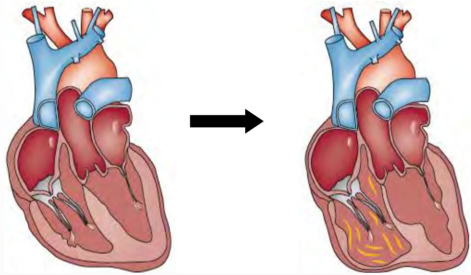
NEXT STEPS

- **Initiation of Pivotal Phase 2 Study**

PKP2-Arrhythmogenic Cardiomyopathy (ACM)*:

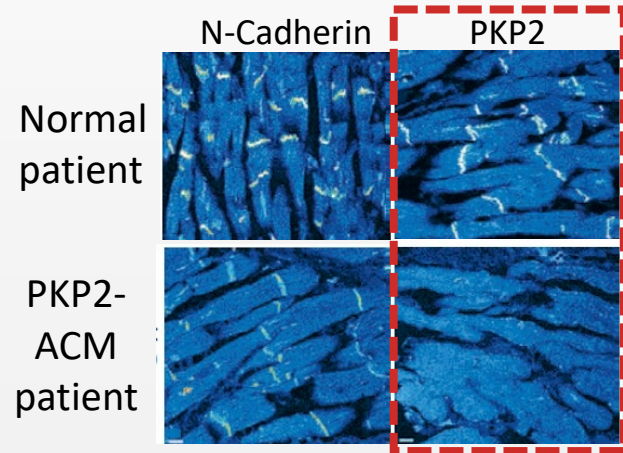
A high-risk disease with no curative options

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

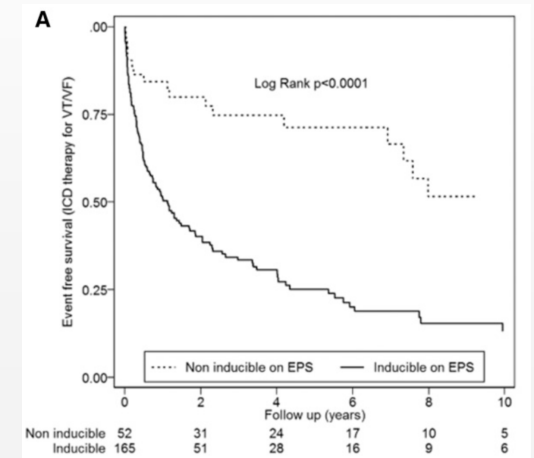
- Current standard of care includes beta-blockers, anti-arrhythmic agents, and ablation
- Available treatments do not modify disease progression; no curative therapeutic options



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 pts⁵
- For pts 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

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

Estimated Prevalence (US+EU): $\sim 50,000$

Biopsy figure adapted from: Asimaki et al. NEJM, 2009; Table adapted from Dalal et al. Circulation 2006. SOC: standard of care; CM: cardiomyopathy; HF: heart failure; HTx: heart transplantation; RV: Right ventricular; SD: Standard Deviation; VT: ventricular tachycardia; LBBB: left bundle branch block; ICD: implantable cardioverter defibrillator; RVEF: right ventricular ejection fraction; LV: left ventricle; SVA: sustained ventricular arrhythmia.

* 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". 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

Peters 2004, McKenna 2021

PKP2 variants

32.9%

2,572 ACM patients assessed from 13 publications an aggregated mean of **32.9% had PKP2 mutations¹**

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

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

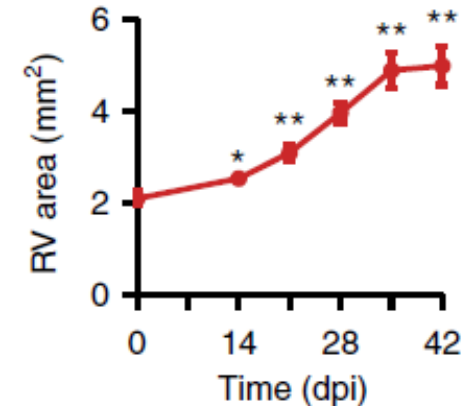
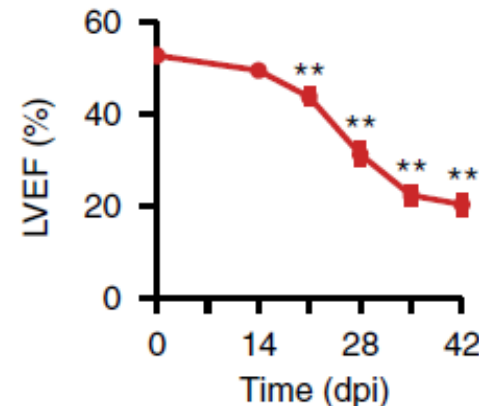
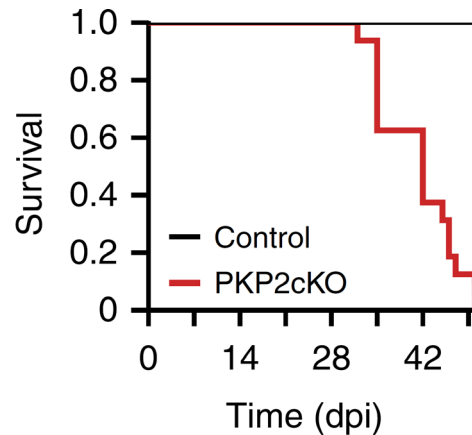
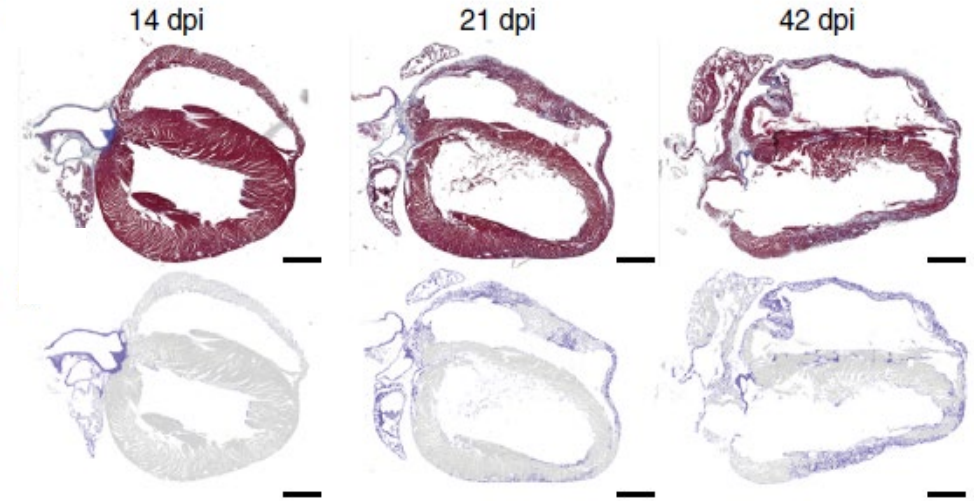
Marina Cerrone, MD

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

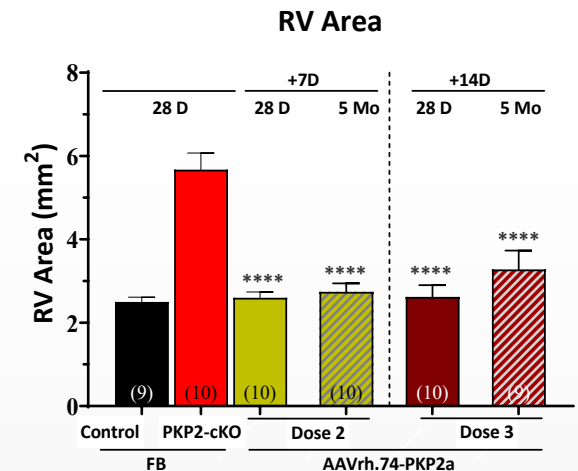
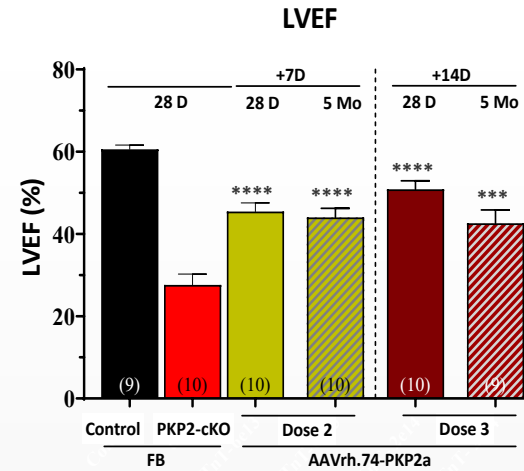
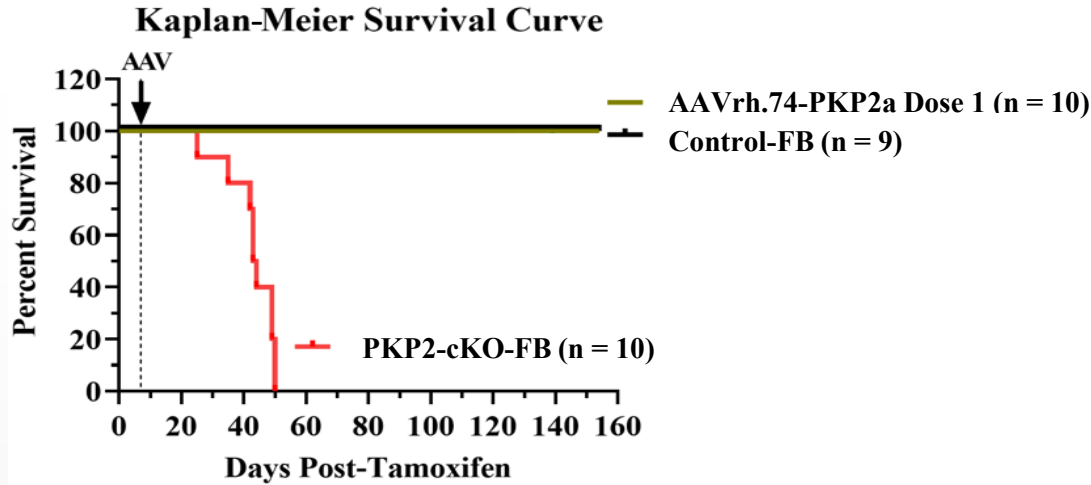
Ongoing sponsored research. No future royalty obligations

Tamoxifen-induced ACM in the PKP2-cKO Mouse Model

- The PKP2-cKO mouse model recapitulates ACM following induction of PKP2 KO by tamoxifen (TAM) injection
- 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 (LVEF) diminishes significantly across time
- Right ventricular (RV) enlargement occurs across time
- Premature Ventricular Contractions (PVCs) are a clinical hallmark of ACM and emerge in the animal model because of Pkp2 loss

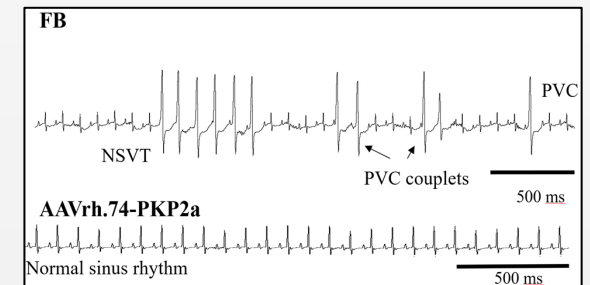
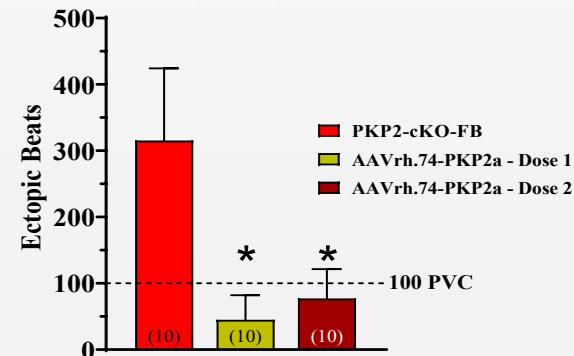


Increased Survival & Preserved Cardiac Function in the PKP2-cKO Model



- 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

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/LGMD2E¹⁻²; 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:

- **Intravenous (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)

¹Rodino-Klapac et. al. Safety, β -Sarcoglycan Expression, and Functional Outcomes From Systemic Gene Transfer of rAAVrh74.MHCK7.hSGCB in LGMD2E/R4. Presented at the Muscular Dystrophy Association (MDA) Conference. Nashville, TN, March 13–16, 2022.

²Mendell et. al. A Phase 2 clinical trial evaluating the safety and efficacy of delandistrogene moxeparvovec (SRP-9001) in patients with Duchenne muscular dystrophy. Presented at the 2022 Muscular Dystrophy Association (MDA) Conference Nashville, TN, March 13–16, 2022.

Clinical Development Plan



Phase 1 Dose Escalation Study

Completed or Ongoing Activities

- ✓ **Phase 1 Study Initiated**
- ✓ **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

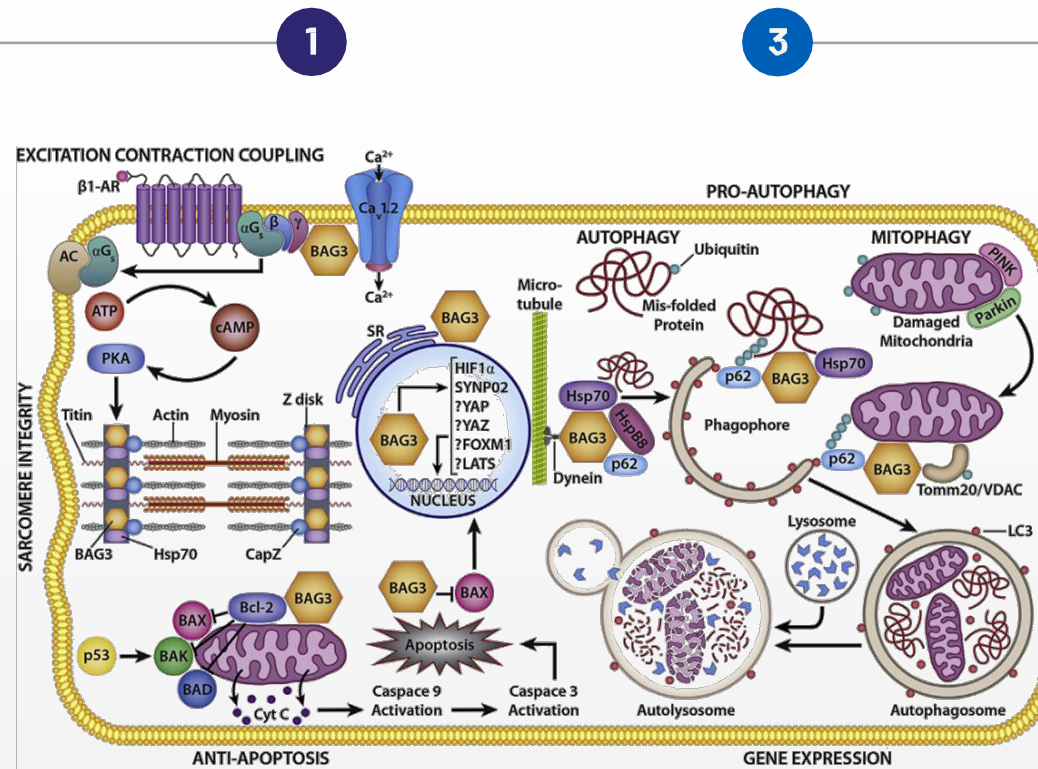
Provides support for the sarcomere by linking actin myofibrils with the Z-disc

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

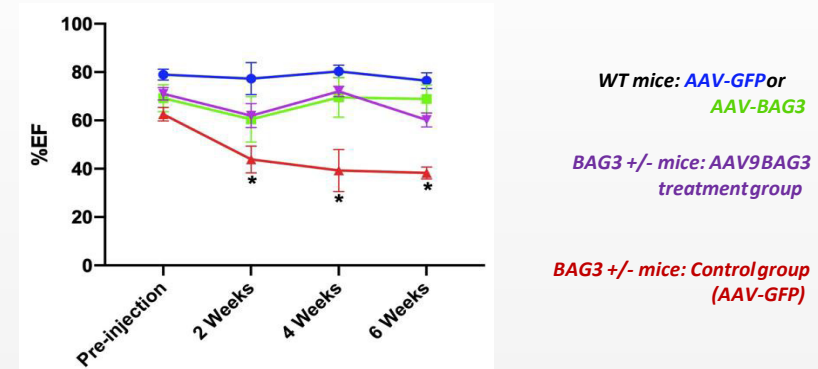
BAG3-DCM Represents a Significant Market with Unmet Need

- Dilated cardiomyopathy (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⁾
- Scientific societies recently endorsed clinical genetic testing for DCM patients and families^(2,3)
- Prevalence of BAG3 DCM in US is estimated to be as high as 30,000 patients⁽⁴⁾ 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 planned for 2024

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, heme 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



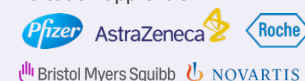
Gaurav Shah, M.D.

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



Isabel Carmona, J.D.

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



Carlos Martin, BA, MBA

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



Aaron Ondrey

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



Raj Prabhakar, MBA

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



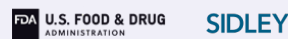
Mayo Pujols

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



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



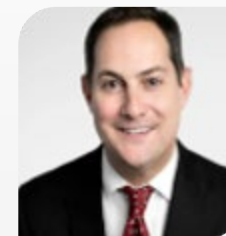
Jonathan Schwartz, M.D.

Chief Medical & Gene Therapy Officer
Led multiple biologics approvals



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





THANK YOU!

