



Extended Results From First-In-Human Clinical Trial Of RP-A501 (AAV9:LAMP2B) Gene Therapy Treatment For Danon Disease

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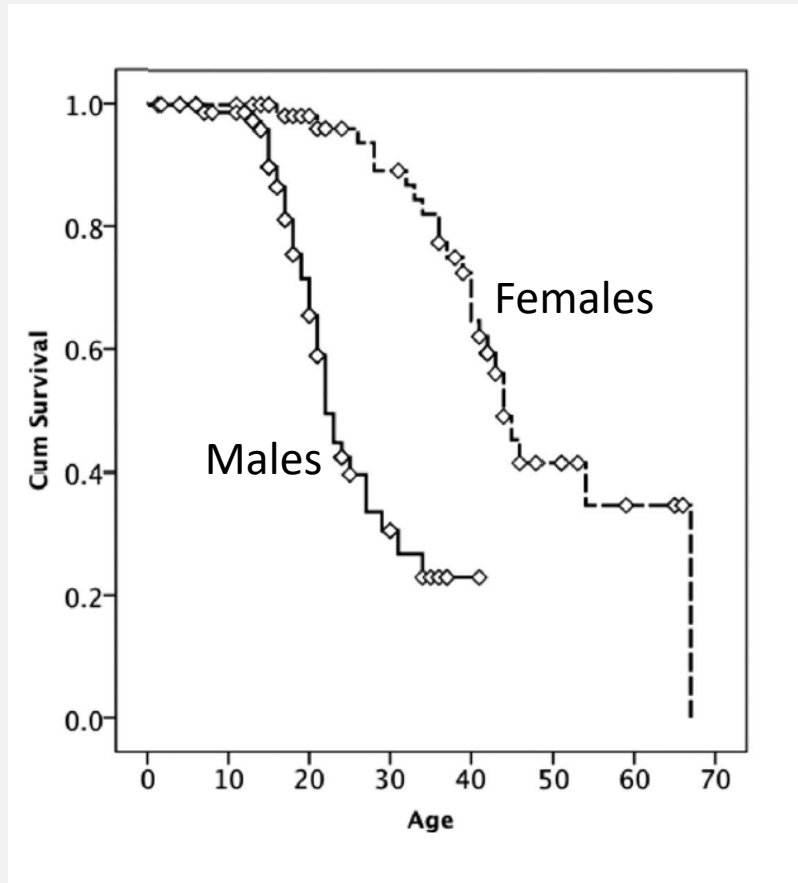
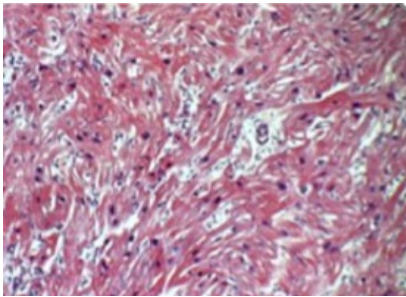
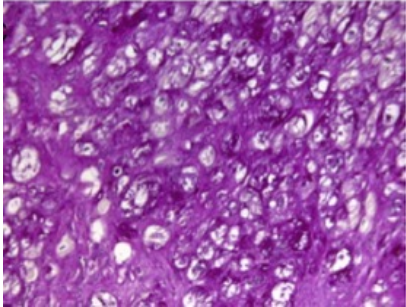
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Abstract # 24



SEEKING GENE THERAPY CURES

Danon Disease



Autosomal dominant, monogenic X-linked disease

- *LAMP-2B* gene mutation
(Lysosomal Associated Membrane Protein 2B)
- Impaired autophagy
 - Prominent sarcoplasmic vacuoles
 - Myocardial disarray

Severe Cardiomyopathy (CM 95%)

- Mortality secondary to heart failure
- **Males:**
 - Hypertrophic CM with arrhythmias
 - Mortality in 2nd to 3rd decades
- **Females:**
 - Dilated/hypertrophic CM and arrhythmias
 - Mortality in 4th to 5th decades

Other Clinical Manifestations

- Skeletal Myopathy
- CNS manifestations
- Ophthalmologic manifestations

Heart transplant is current standard of care

RP-A501: Danon Disease Gene Therapy Clinical Trial Overview

Design

**Non-
Randomized
Open Label
Phase 1
Study**

- Male Danon Disease patients
 - Adults (& Adolescents): ≥ 15 years
 - Pediatric: 8-14 years
- Single Intravenous Dose of **RP-A501 (AAV9.LAMP2B)**
 - Low Dose: 6.7×10^{13} GC/kg
 - High Dose*: 1.1×10^{14} GC/kg

Primary Outcomes

- **Safety at each dose level**
- Target tissue transduction & *LAMP2B* expression
- Effect on cardiomyocyte morphology
- Clinical stabilization or improvement

Key Patient Entry Criteria**

Inclusion

- Male
- Confirmed *LAMP2B* mutation
- Cardiac involvement confirmed by imaging or ECG
- New York Heart Association (NYHA) Class II or III
- Able to walk >150 meters unassisted during 6-minute walk test (6MWT)

Exclusion

- Anti-AAV9 neutralizing antibodies
- Cardiopulmonary instability
- Prior organ transplantation

* No further enrollment at this dose.

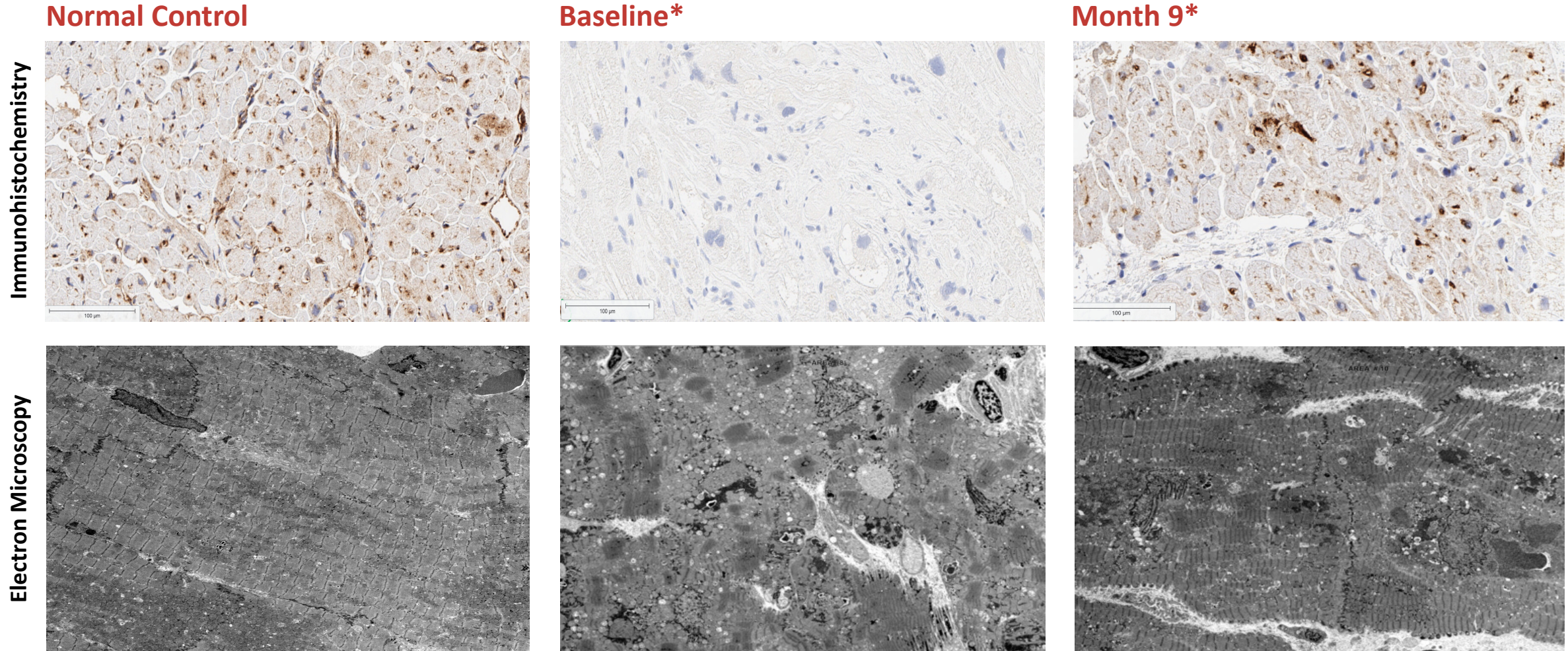
** Additional details at ClinicalTrials.gov

RP-A501: Baseline Status of Adult Cohorts

Cohort	Patient ID	Age at Enrollment (years)	Weight (kg)	Clinical Status		Cardiac Status	
				NYHA Class	Six Minute Walk (meters)	BNP (pg/mL)	LV Ejection Fraction* (%)
Adult - Low Dose 6.7 x 10 ¹³ GC/kg	1001	17.5	52.5	II	443	70	62
	1002	20.4	89.1	II	405	942	59
	1005	18.3	91.8	II	427	176	59
Adult - High Dose 1.1 x 10 ¹⁴ GC/kg	1006	21.1	82.7	II	436	123	47
	1007	20.7	96.7	II	434	630	35

*All echocardiographic parameters are from local laboratory assessment by a single reader.
BNP = Brain Natriuretic Peptide
NYHA = New York Heart Association

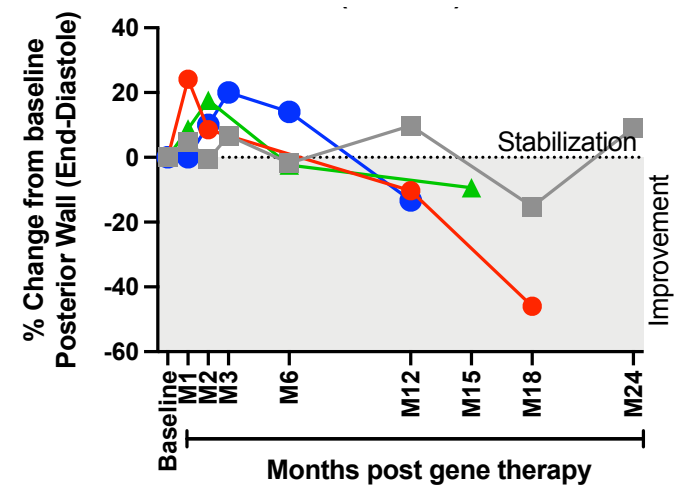
RP-A501: LAMP2 Cardiac Protein Expression by Immunohistochemistry and Myofibrillar Structure by Electron Microscopy



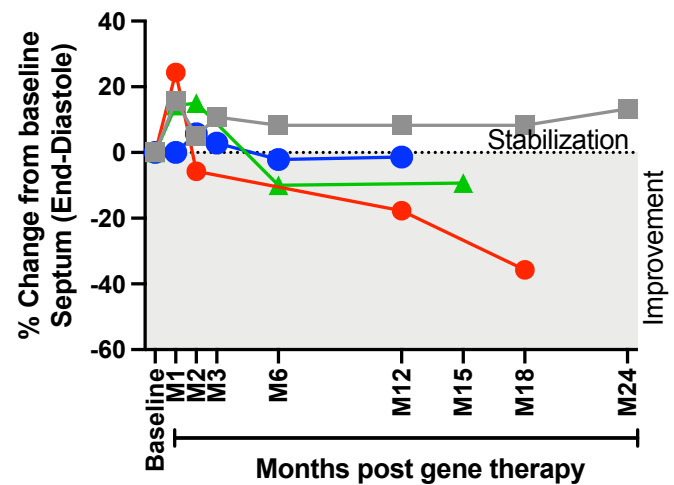
*Representative images from patient 1005 from endomyocardial biopsy.

RP-A501: Remodeling of Left Ventricular Hypertrophy in Adult Cohorts

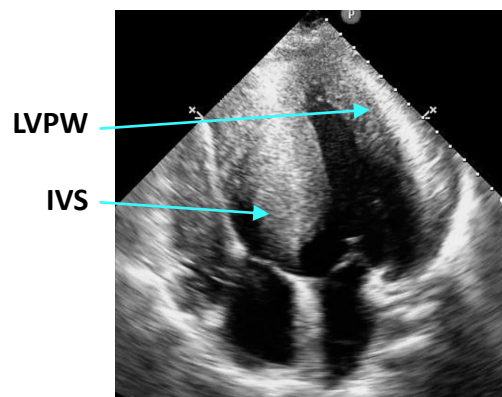
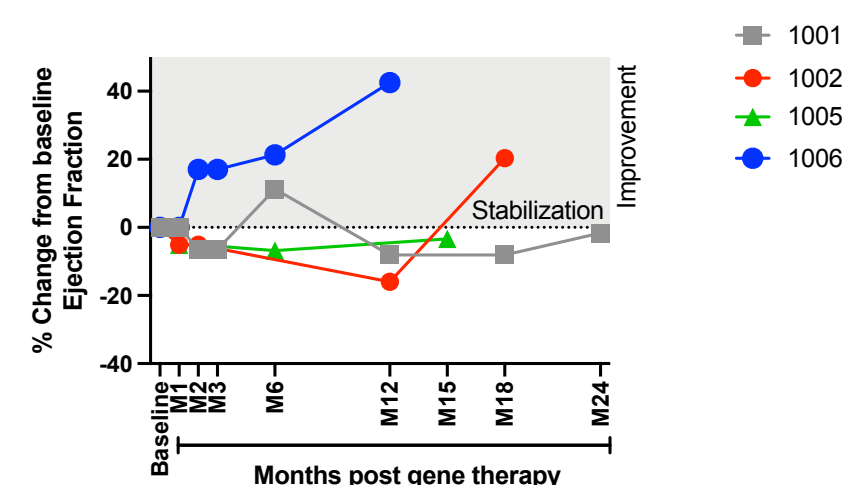
Posterior Wall Thickness (LVPWd)



Septum Thickness (IVSd)



Ejection Fraction (LV EF)



Baseline



Month 15

Representative
images from
patient 1005

All echocardiographic parameters are from local laboratory assessment by a single reader.

RP-A501: Functional Clinical Status of Adult Cohorts

Cohort	Patient ID	Variable	Baseline	Most Recent Follow-up	Time of Follow-up
Adult – Low Dose	1001*	NYHA class	II	II	24 Months
		BNP (pg/mL)	70	30	
	1002	NYHA class	II	I	18 Months
		BNP (pg/mL)	942	200	
	1005	NYHA class	II	I	15 Months
		BNP (pg/mL)	176	44	
Adult – High Dose **	1006	NYHA class	II	I	12 Months
		BNP (pg/mL)	123	41	

* Corticosteroid compliance uncertain.

** Patient 1007 underwent heart transplant at 5 months for progressive DD, thus no subsequent data reported.

BNP = Brain Natriuretic Peptide

NYHA = New York Heart Association

RP-A501: Grade 3 and 4 Serious Adverse Events (SAEs) in Adult Cohorts (As Previously Disclosed)

RP-A501 Related*:

Thrombotic microangiopathy (TMA) [grade 4] associated with

- thrombocytopenia [grade 4]
- acute kidney injury & renal failure [grade 4]

Transaminase increase [grade 3]

n=3; transient and resolved with immunosuppression

Pt 1007 (received highest dose secondary to baseline weight and 1.1×10^{14} GC/kg dose level)

Resolved fully with eculizumab and temporary hemodialysis

Corticosteroid Related*:

Skeletal myopathy [grade 3]

- n=3; resolved with steroid taper

Salmonella sepsis [grade 3]

- n=1; resolved with antibiotics

Danon Disease Progression Likely Related*:

Acute cardiac failure with ventricular arrhythmia [grade 4]

Pt 1007 (LVEF 35% at enrollment)

Based on MedDRA v23; the highest severity for each event (per NCI-CTCAE v.5.0) is presented.

*Indicates events for which the relationship was definitely, probably, or possibly related.

RP-A501: Risk Mitigation Strategies Implemented Prior to Pediatric Enrollment

Enhanced prophylactic immunosuppressive regimen

- Sirolimus to inhibit complement activation
- Steroid-sparing regimen to decrease skeletal myopathy
 - Initial dose 0.5 to 0.8 mg/kg/day (compared to ≥ 1 mg/kg/day in adult cohort)
 - Early initiation of taper (Day 10) and discontinuation (goal Month 3)
- Enhanced monitoring for early signs of TMA for potential early use of Eculizumab
 - Clinical Monitoring Team included 2 independent monitors with expertise in TMA

Dose-dependent toxicity

- No further enrollment at higher dose level

RP-A501: Immunosuppression, Patient Characteristics & Safety in Phase 1

Cohort 1: Low-dose adult

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

RP-A501
 6.7×10^{13} GC/kg

Steroid (prednisone 1mg/kg)

Tacrolimus

SAEs of Interest

n=2 grade 3 steroid myopathy

Platelets

n=2 decreases to LLN range

Cohort 2: High-dose adult

Pt	Age	Wt
1006	21.1	82.7
1007	20.7	96.7

RP-A501
 1.1×10^{14} GC/kg

Steroid (prednisone 1mg/kg)

Tacrolimus

Rituximab

n=1 grade 4 TMA

n=1 grade 3 steroid myopathy

n=1 grade 4 decrease

Cohort 3: Low-dose pediatric

Pt	Age	Wt
1008	12.3	70.5
1009	11.5	55.7

RP-A501
 6.7×10^{13} GC/kg

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

Sirolimus

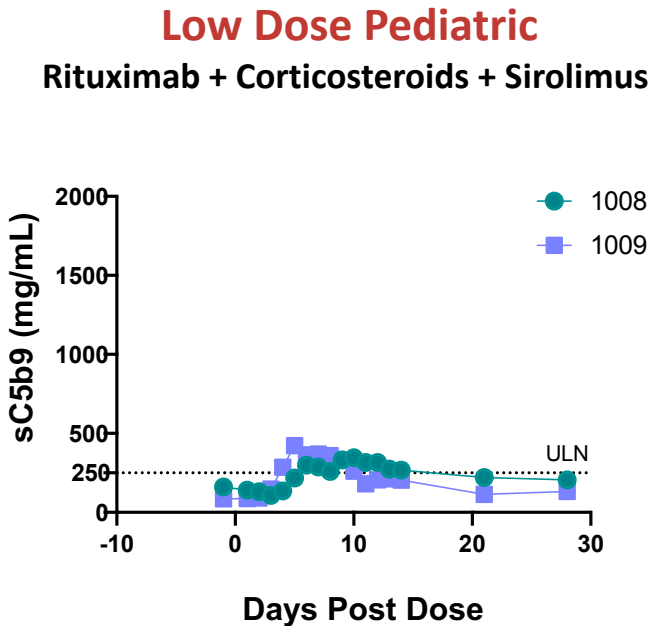
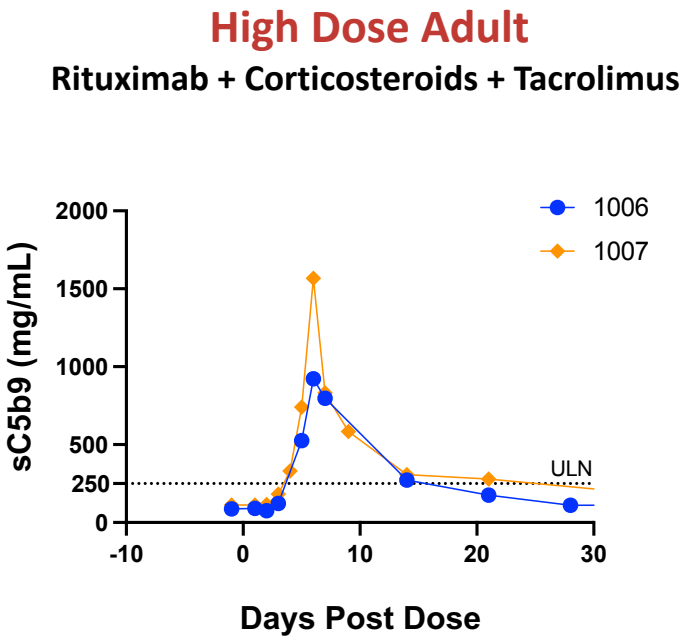
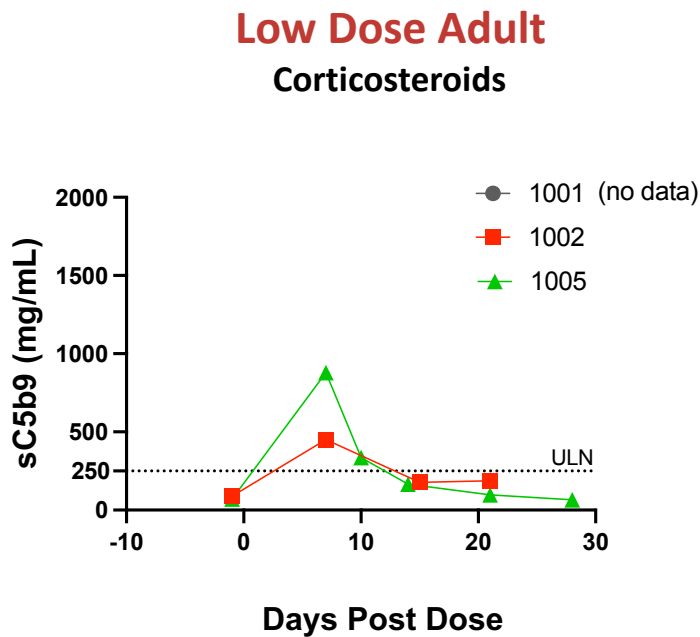
Rituximab

none

n=2 normal range

RP-A501: Inhibition of Complement Activation with Modified Immunosuppression

sC5b9
(terminal soluble complement complex)



Platelets

2 of 3 patients had platelet decreases to LLN range

1 of 2 patients (Pt 1007) had grade 4 thrombocytopenia (transient)

2 of 2 patients had platelets remain within normal range

RP-A501: Summary of Results from Adult and Pediatric Cohorts

Adult Cohort:

- RP-A501 was generally well tolerated
- Increased LAMP2 protein expression with signals of disease stabilization and improvement including NYHA class, BNP, wall thickness and cardiac histology

Pediatric Cohort: RP-A501 was well tolerated in both patients with modified protocol

- T- and B-cell directed immunosuppression associated with markedly reduced complement activation relative to adult cohorts
 - **Minimal complement activation**
 - **Platelets remained within normal range**
 - **No complement-related clinical or laboratory AEs**
- Absent or limited worsening of skeletal myopathy with initial steroid dose-reduction and more rapid taper, and introduction of sirolimus
- No immediate, early or delayed RP-A501 related toxicities observed to date

RP-A501: Conclusion and Future Direction

- RP-A501 was generally well tolerated in adult and pediatric patients with Danon disease
- Modified immunosuppressive regimen appears well tolerated and effective in pediatric cohort
- Phase 1 efficacy signal in age ≥ 15 cohort: RP-A501 stabilizes and potentially improves Danon disease cardiomyopathy
- These findings support phase 2 evaluation of RP-A501 in Danon disease

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