Lentiviral-Mediated Ex-Vivo Gene Therapy for Pediatric Patients with Severe Leukocyte Adhesion Deficiency-I (LAD-I): Interim Results from an ongoing Phase 1/2 Study

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Disclosures

I am a paid member of the Scientific Advisory Boards of:

- Allogene Therapeutics
- Pluto Therapeutics
- ImmunoVec
- MyoGeneBio

Leukocyte Adhesion Deficiency-I (LAD-I)

LAD-I

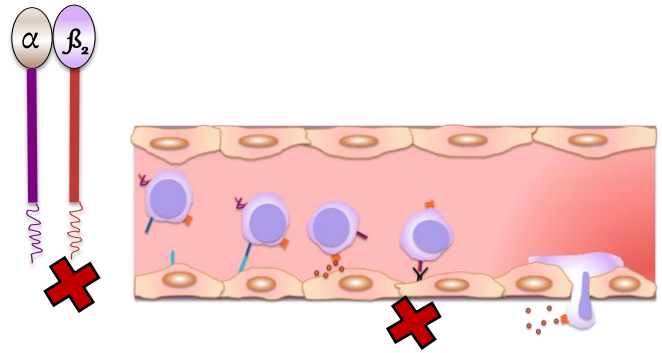
- Mutations affect the common chain (CD18) of the beta2-integrin family (*ITGB2* gene) and prevent functional CD18/CD11 heterodimer expression on leukocyte cell surfaces – essential for cell adhesion and subsequent migration.
- Severe LAD-I is characterized by *recurrent and ultimately fatal disseminated infections*.
- Current Treatment Option: Allogeneic HSCT – limited by donor availability, infections, frequent GvHD and graft failure.

LAD-I Disease Spectrum

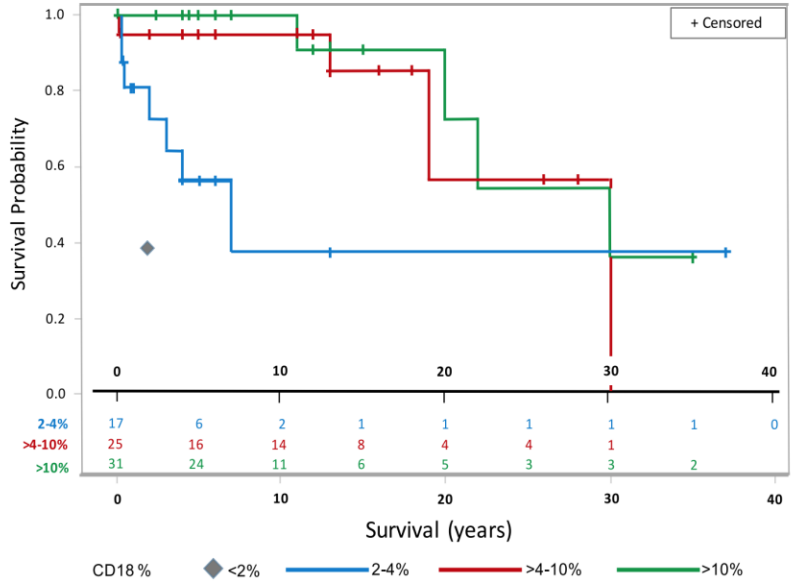
Moderate: 2–30% CD18+ PMN ⟷ Severe: <2% CD18+ PMN

Clinical Prognosis

- Patients suffer from recurrent infections; fatal in majority
  - 60–75% pts with severe LAD-I: death **prior to age 2**
  - >50% pts with moderate LAD-I: death **prior age 40**



Kaplan-Meier Survival Estimates by Neutrophil CD18 Expression



Patients with severe and moderate LAD-I not receiving allogeneic HSCT

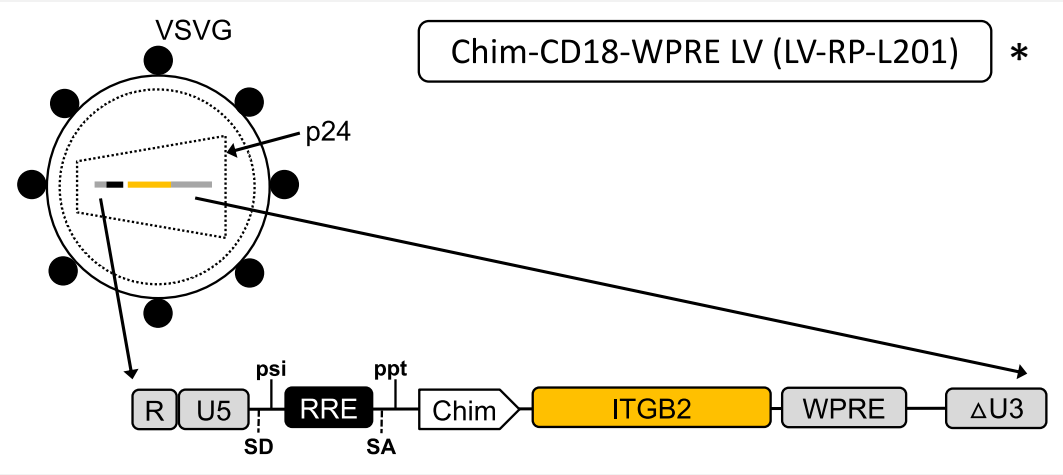
◆ : **39% survival to age 2 years** for 66 evaluable patients with severe LAD-I not receiving HSCT

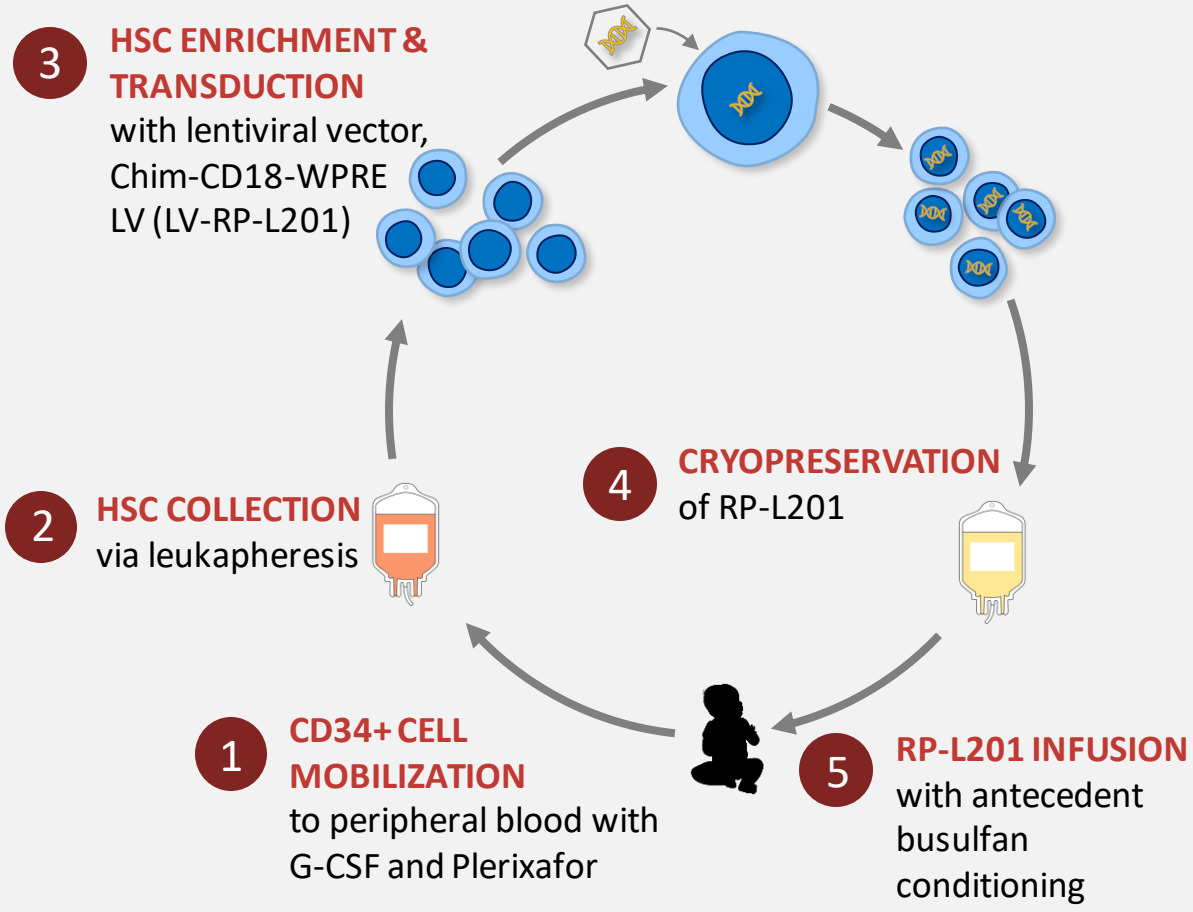
HSCT: hematopoietic stem cell transplantation; PMN: polymorphonuclear leukocytes

Almarza E et al. J Allergy Clin Immunol Pract. 2018 July-August (6) 1418-1420.

Gene Therapy for LAD-I: RP-L201

***Ex-vivo* lentiviral vector gene therapy consists of autologous CD34+ cells transduced with a lentiviral vector (Chim-CD18-WPRE LV) encoding the CD18 (β-subunit) component of the β2-integrin receptor family.**





*Developed at CIEMAT in partnership with UCL

CIEMAT: Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas, Madrid, Spain

UCL: University College London / Great Ormond Street Institute of Child Health, London, UK

RP-L201 Clinical Trial Design, Patient, and Drug Product Characteristics

Trial Design

- Non-Randomized Global Phase 1/2 Study (n=9)

Key Eligibility Criteria

- Severe LAD-I; CD18 expression <2% PMNs, or CD11a/b <2% with documented *ITGB2* mutation
- Age ≥3 months
- At least one prior significant bacterial of fungal infection

Primary Outcomes

Phase 1:

- Safety and preliminary efficacy

Phase 2:

- Survival: Proportion of patients alive at age 2 and at least 1-year post infusion (and not requiring allogeneic HSCT)
- Safety

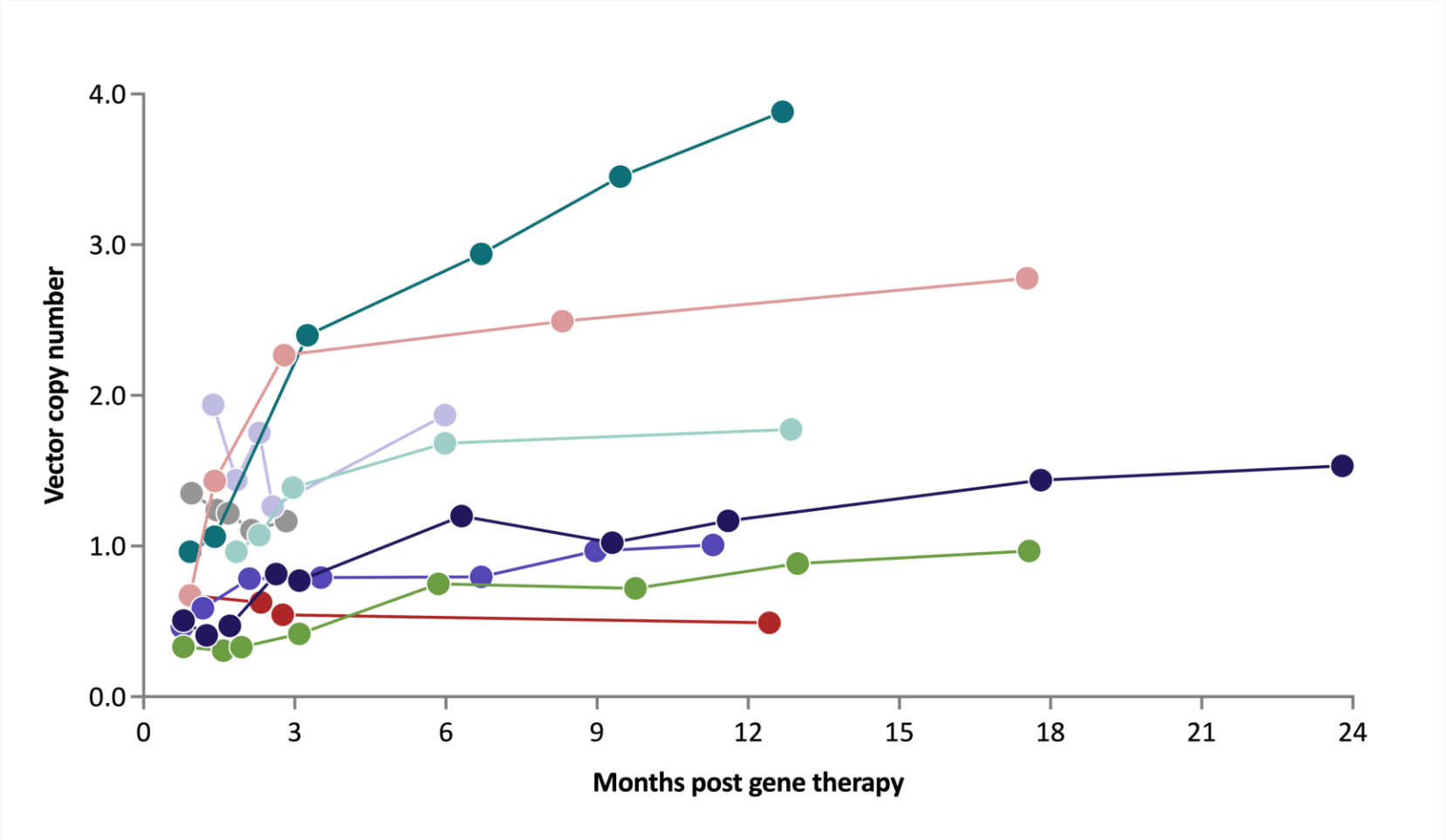
Secondary Outcomes

- **Incidence and severity of infections** (e.g., incidence of severe infections, hospitalizations and prolonged hospitalizations)
- % of patients **with neutrophil CD18 expression at least 10% of normal**
- % of patients with neutrophil **VCN** of at least 0.1 at 6m post-infusion
- Improvement/**normalization of leukocytosis**
- Resolution (partial or complete) of underlying **skin rash or periodontal abnormalities**

Patient	Sex	Age at enrollment	Drug Product VCN	CD34+ Cell Dose
L201-003-1001	F	9 years	3.8	4.2×10^6 cells/kg
L201-003-1004	F	3 years	2.5	2.8×10^6 cells/kg
L201-003-2005	F	3 years	1.8	6.5×10^6 cells/kg
L201-003-2006	M	7 months	2.9	4.3×10^6 cells/kg
L201-003-2007	M	3 months	3.6	5.0×10^6 cells/kg
L201-004-2008	M	5 months	3.8	3.3×10^6 cells/kg
L201-004-2009	M	3 years	2.0	4.5×10^6 cells/kg
L201-002-2010	F	4 years	3.5	10.0×10^6 cells/kg
L201-003-2011	F	2 years	3.8	3.8×10^6 cells/kg

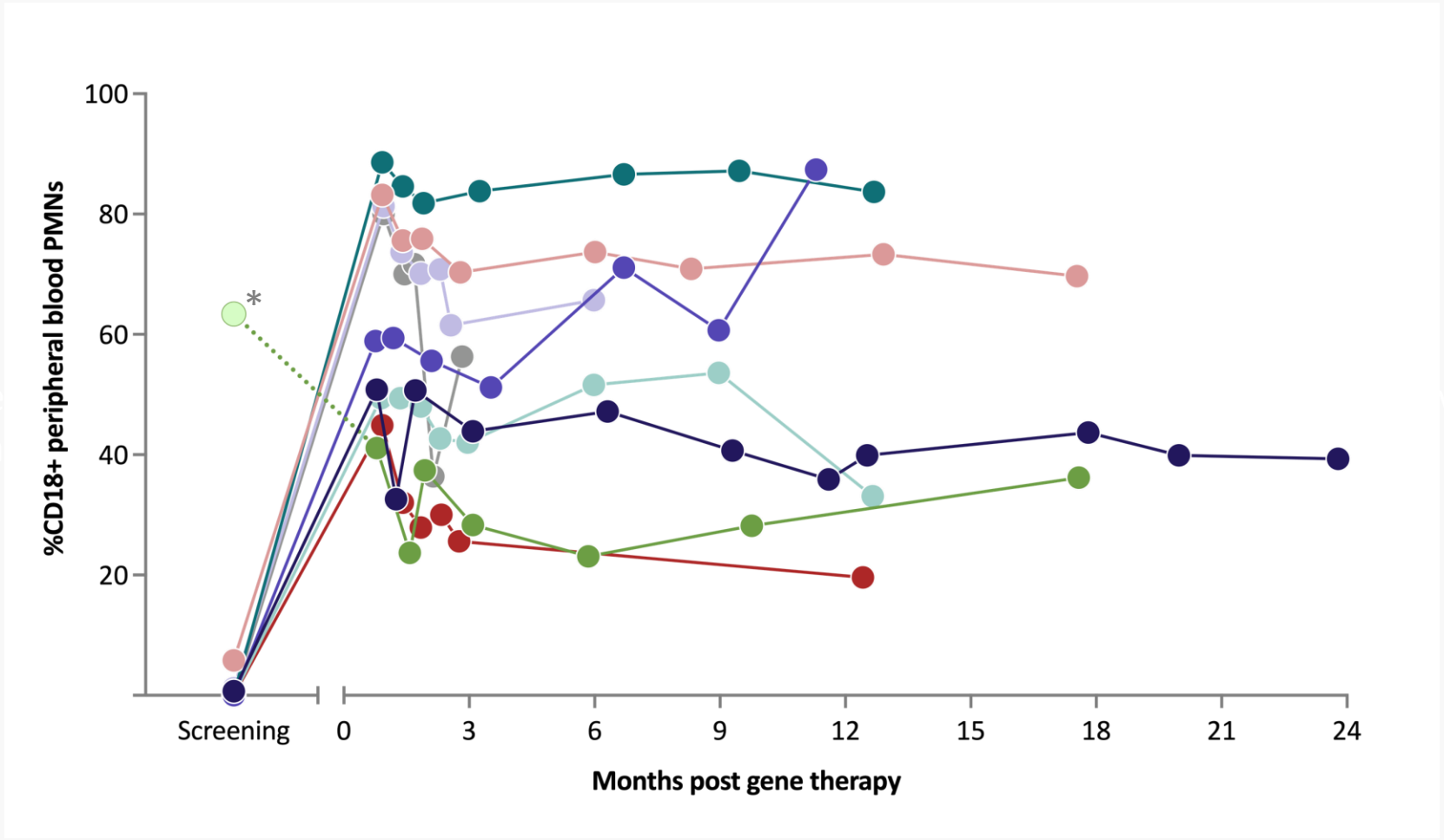
As of April 6, 2022: Data reported from 9 of 9 patients (3–24m follow-up).
Study enrollment is completed. All subjects have been treated.

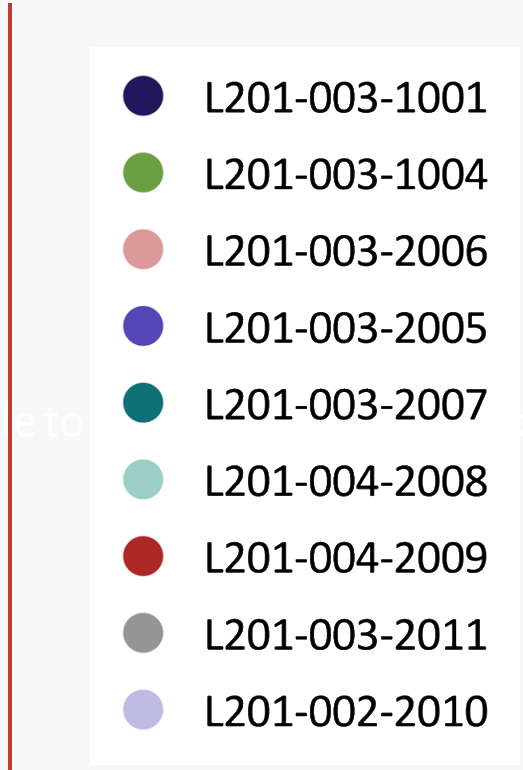
VCN in Peripheral Blood Mononuclear Cells (PBMCs)



Data cut-off: April 6, 2022; Preliminary interim results are presented from the ongoing clinical study.

CD18 Expression in PB Polymorphonuclear Cells (PMNs)



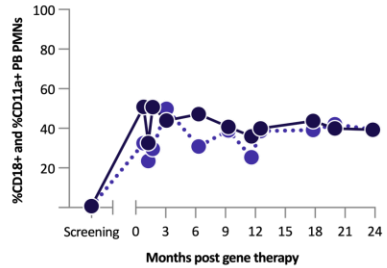


* Dim/weak CD18 expression reported at baseline for Subject L201-003-1004 in ~63% of cells in conjunction with <2% CD11a/CD11b expression, likely indicating abnormal/unstable protein

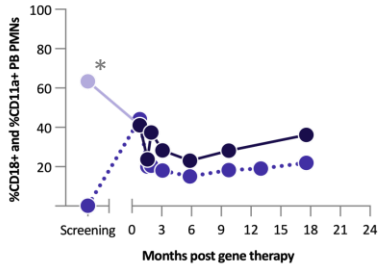
Data cut-off: April 6, 2022; Preliminary interim results are presented from the ongoing clinical study.

CD18 and CD11a Expression in PB PMNs

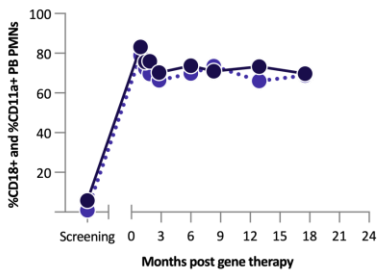
L201-003-1001



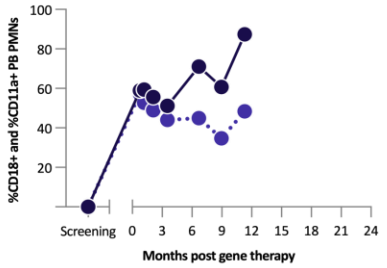
L201-003-1004



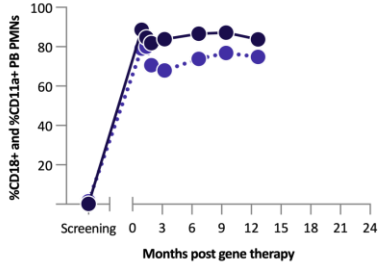
L201-003-2006



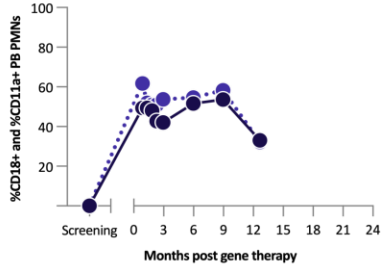
L201-003-2005



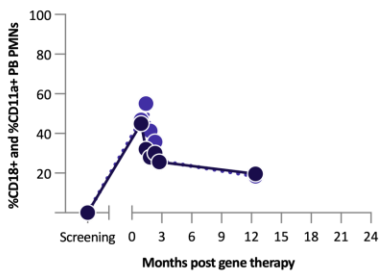
L201-003-2007



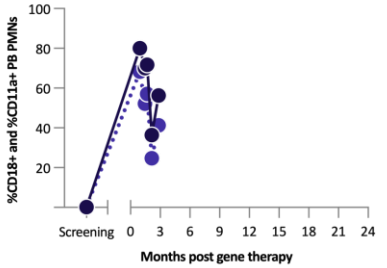
L201-004-2008



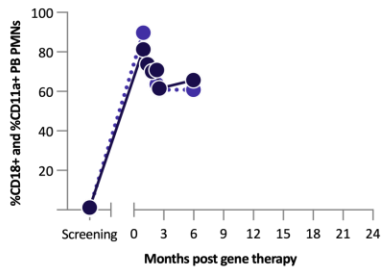
L201-004-2009



L201-003-2011



L201-004-2010



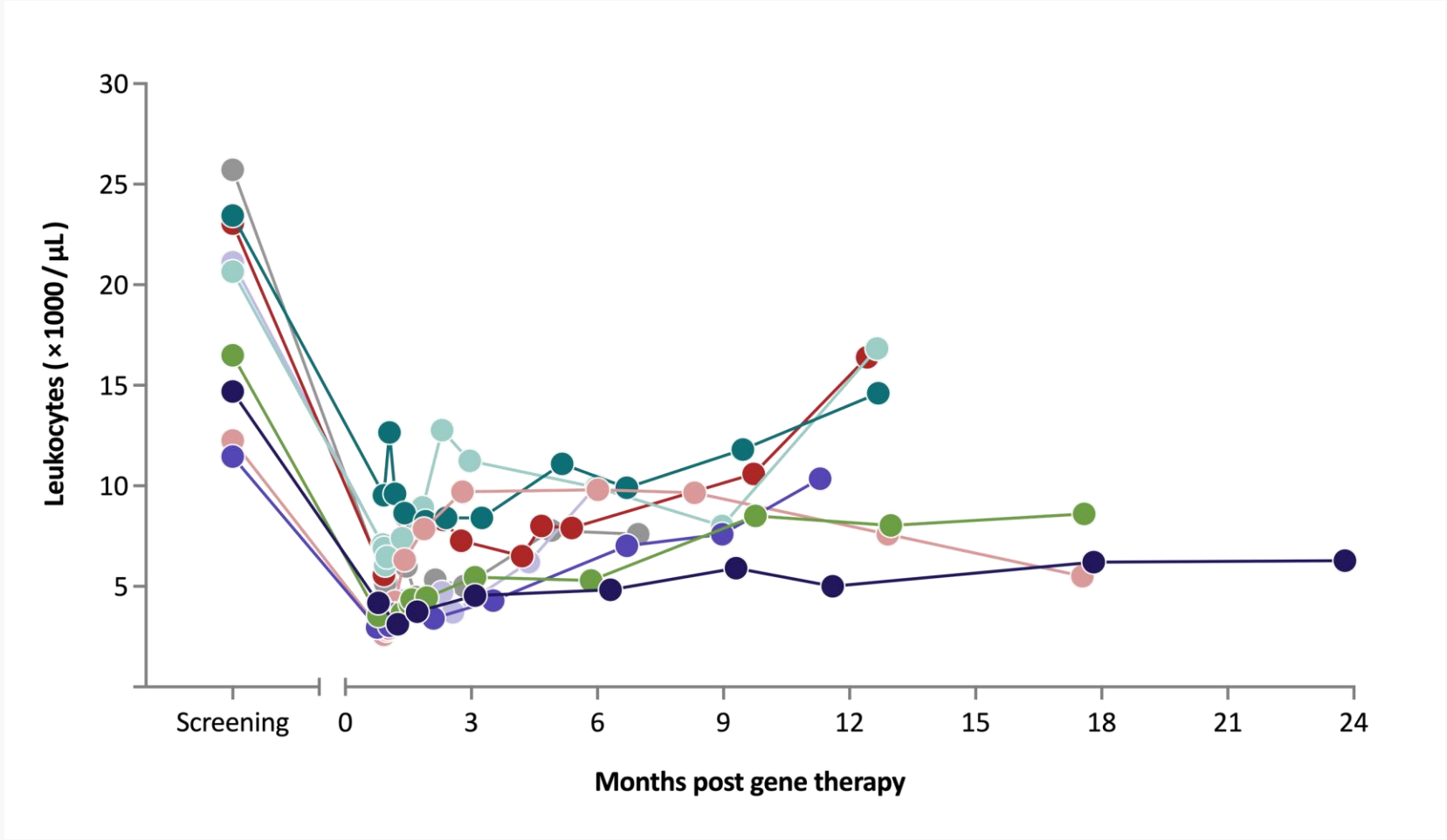
%CD18+ Expression

%CD11a+ Expression

* 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

Data cut-off: April 6, 2022; Preliminary interim results are presented from the ongoing clinical study.

Resolution of LAD-I Related Abnormal Leukocytosis: A clinical biomarker of a normalized phenotype



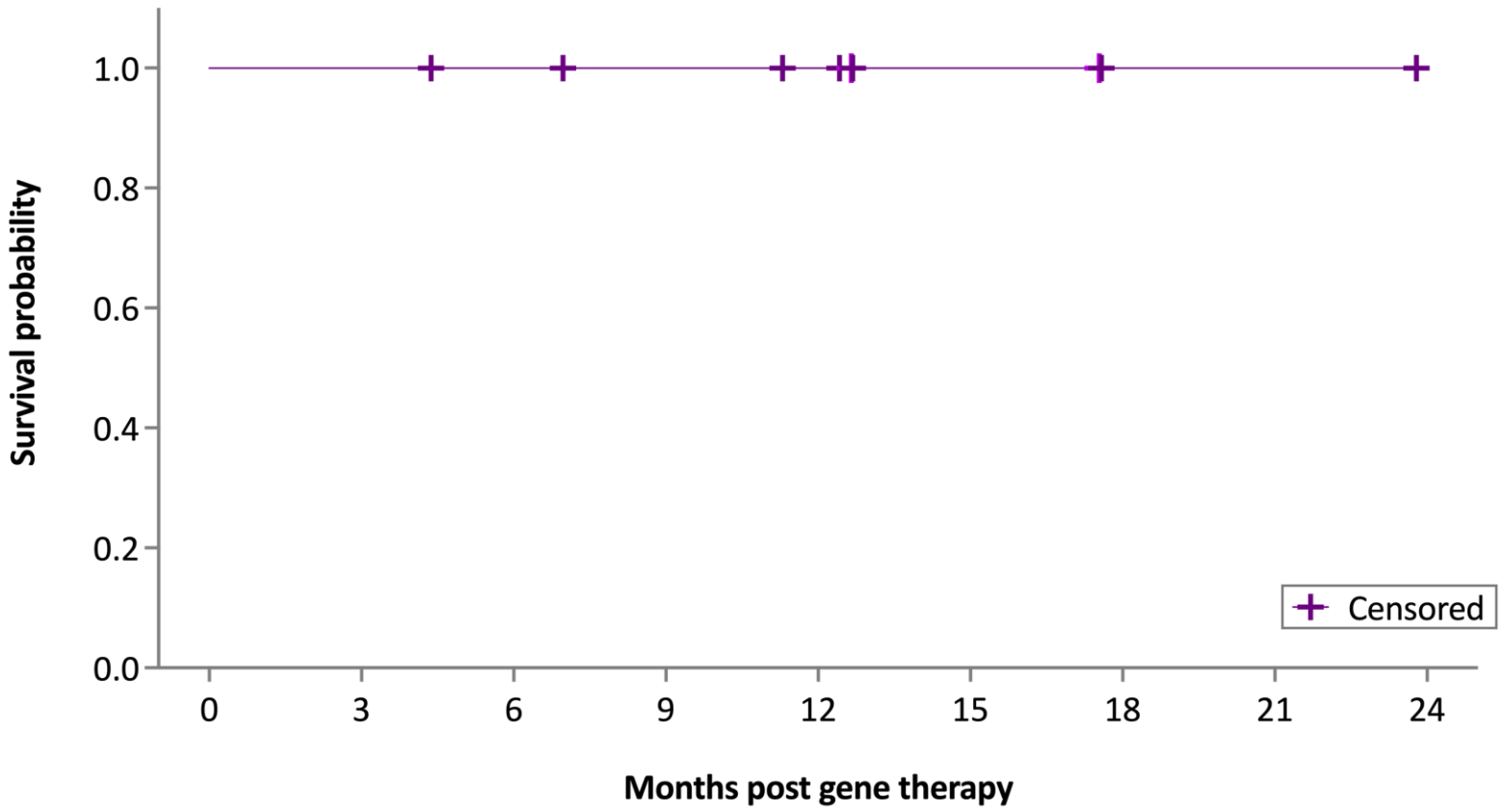
Age at Enrollment

- L201-003-1001 (9y)
- L201-003-1004 (3y)
- L201-003-2006 (7mo)
- L201-003-2005 (3y)
- L201-003-2007 (3mo)
- L201-004-2008 (5mo)
- L201-004-2009 (3y)
- L201-003-2011 (2y)
- L201-002-2010 (4y)

Normal Leukocyte Ranges per Age Group: *0 months to <3 months: 7.20–18.00×1000/µL; ≥3 months to <6 months: 6.70–14.00×1000/µL; ≥ 6months to 12 months: 6.40–13.00×1000/µL; 12 months to <2 years: 6.40–12.00×1000/µL; ≥2 to <6 years: 5.20–11.00×1000/µL; ≥6 years to <12 years: 4.40–9.50×1000/µL; ≥12 years to <18 years: 4.40–8.10×1000/µL*

Data cut-off: April 6, 2022; Preliminary interim results are presented from the ongoing clinical study.

100% Overall Survival one-year post-RP-L201 and to 2 years of age



Survival without allogeneic HSCT

Primary Outcomes

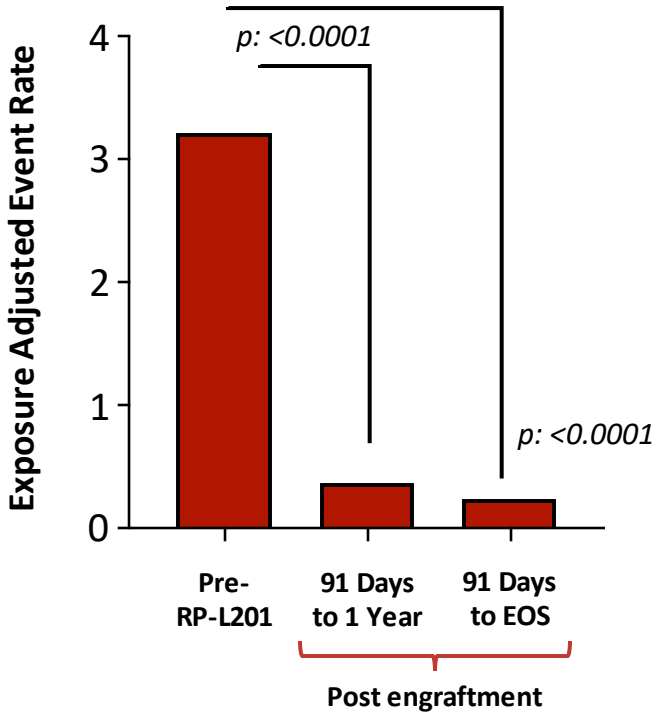
- >2 years of age
- 1-year post-RP-L201 infusion

Data cut-off: March 9, 2022; Preliminary interim results are presented from the ongoing clinical study.

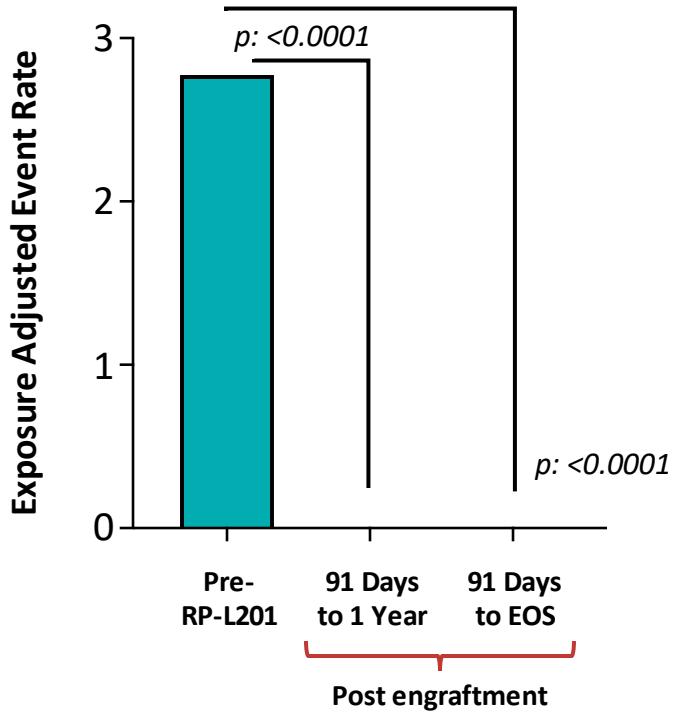
RP-L201 Clinical Outcome Measures

Incidence of All Hospitalizations and Infection and Inflammatory Related Hospitalizations

Incidence of Hospitalizations



Incidence of Infection and Inflammatory Related Hospitalizations

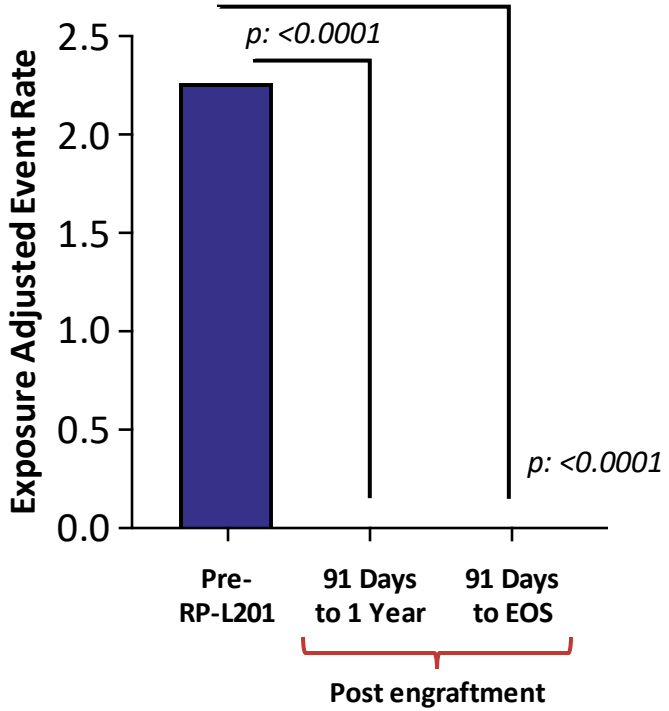


EOS: end of study

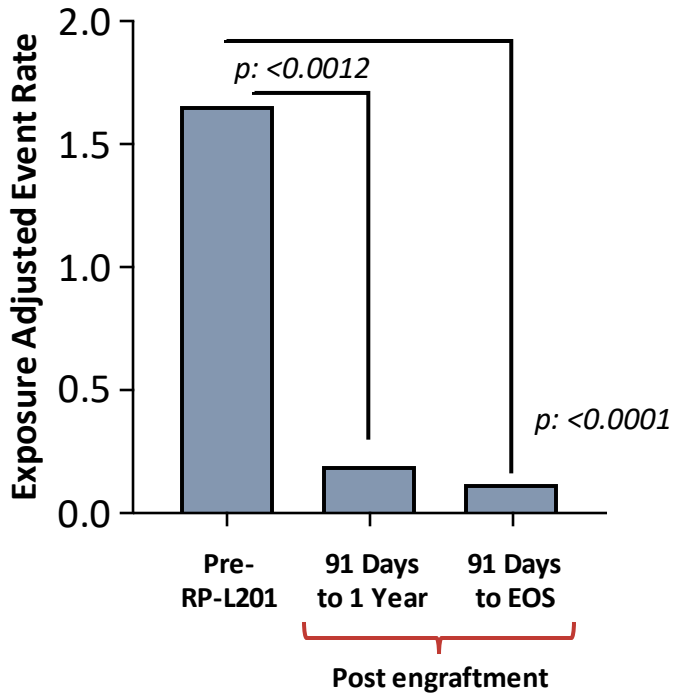
RP-L201 Clinical Outcome Measures

Incidence of Prolonged Hospitalizations and Severe Infections

Incidence of Prolonged (>7 days) Hospitalization



Incidence of Severe Infections



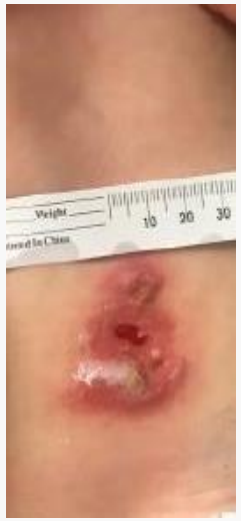
EOS: end of study

Spontaneous LAD-I Related Skin Rash Resolution and Restoration of Wound Repair Capabilities after RP-L201

Spontaneous resolution of abdominal lesion

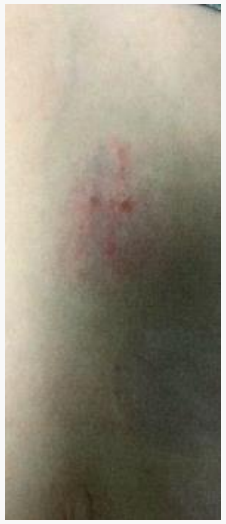
L201-003-1001

Baseline



3 months Post-RP-L201

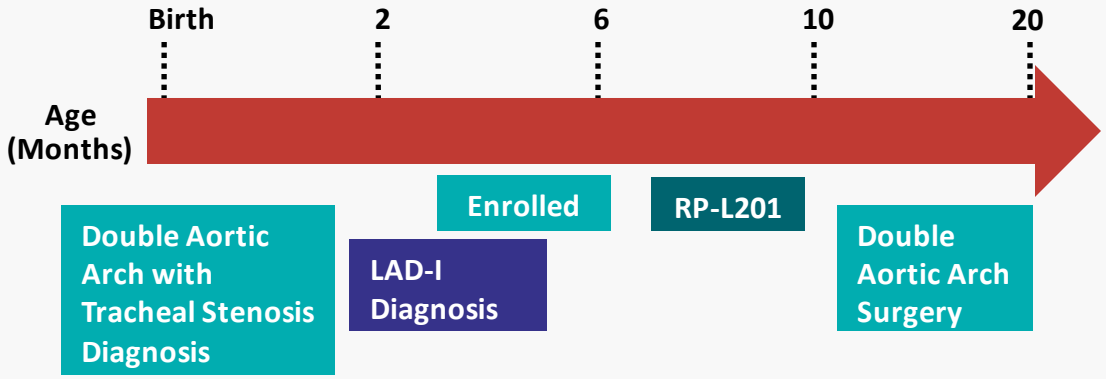
6 months Post-RP-L201

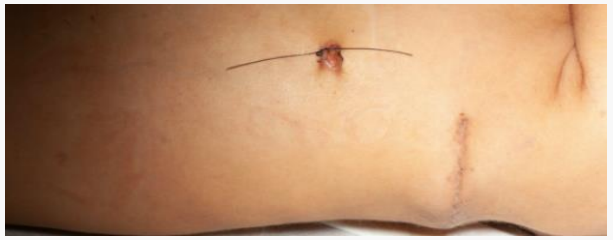


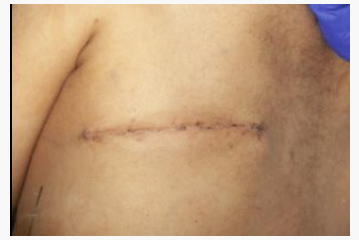
12 months Post-RP-L201

Wound repair at thoracotomy site after surgical correction of double aortic arch

L201-004-2008







Clinical Safety Overview

As of April 6, 2022, **nine** severe LAD-I patients have received RP-L201.

Data is available from **9/9** patients with 3–24 m follow-up.

- **To date, no RP-L201 related adverse events have been reported.**
- **Neutrophil engraftment** achieved in **9/9** subjects (<34 days post-infusion)
- Adverse events related to other study procedures (including busulfan conditioning) have been consistent with the safety profiles of those agents and procedures.
  - **Conditioning-related SAE**: Veno-occlusive disease (**VOD**), resolved with no subsequent complication
  - **Conditioning- and LAD-I related SAE**: Grade 4 pulmonary arterial hypertension (**PAH**), considered secondary to busulfan in the context of damaged pulmonary milieu due to severe pre-treatment pneumonias. In addition to severe LAD-I, patient had double aortic arch associated with tracheal compression.
    - PAH resolved; patient subsequently underwent successful **surgical correction of double aortic arch**.

RP-L201 Clinical Safety & Efficacy Overview

- **All** (9/9) severe LAD-I patients have successfully received RP-L201; currently with 3–24 months follow-up
- Infusion has been **well tolerated**; no drug product-related SAEs
- Safety profile of RP-L201 appears favorable
- Initial **ISA** indicates **highly polyclonal patterns** without evidence of dominant integrations in proximity to oncogenic *loci*
- Efficacy evident in **9/9** patients, including **7** patients with **≥12 months** of follow-up
  - **Sustained** >10% **CD18 PMN expression** (Range: 87.4%–19.6%, Median: 56.3%), concomitant sustained **CD11 expression,** >0.1 **VCN** integration and **leukocytosis** resolution across the cohort
  - **100% overall survival** including 100% OS one-year post-RP-L201 and to 2 years of age
  - Significant **reduction** in all **hospitalizations**, infection and inflammatory related hospitalizations, prolonged hospitalizations, and **severe infections**
  - Evidence of spontaneous **resolution** of LAD-I related **skin rash** and **restoration of wound repair** capabilities

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