



Interim Results From an Ongoing Phase 1/2 Study of Lentiviral-Mediated *Ex-Vivo* Gene Therapy for Pediatric Patients with Severe Leukocyte Adhesion Deficiency-I (LAD-I)

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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) & prevent functional CD18/CD11 heterodimer expression on leukocyte cell surfaces – essential for cell adhesion and subsequent migration.
- Severe LAD-I is characterized by recurrent & ultimately fatal disseminated infections.
- Current Treatment Option: Allogeneic HSCT – limited by donor availability, infections, frequent GvHD and graft failure.

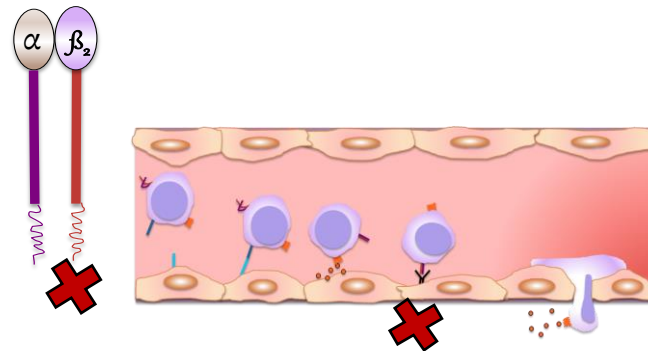
LAD-I Disease Spectrum

Moderate: 2–30%
CD18⁺ PMN

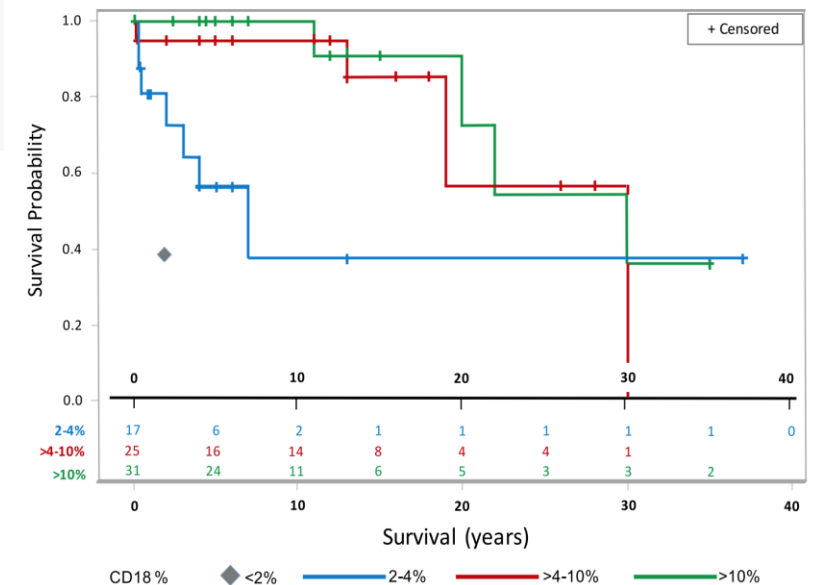
Severe: <2%
CD18⁺ PMN

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 & moderate LAD-I not receiving allogeneic HSCT

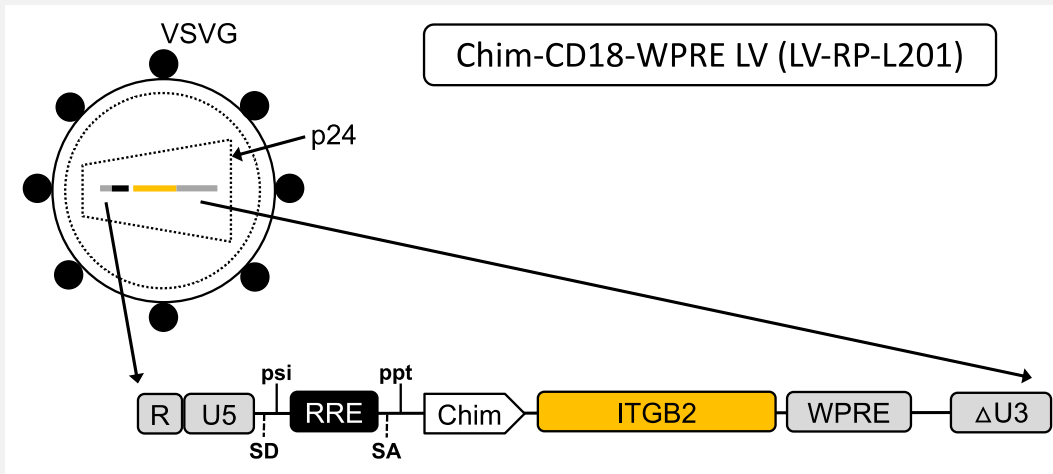
◆ : 39% survival to age 2 years for 66 evaluable patients with severe LAD-I not receiving HSCT

PMN: polymorphonuclear leukocytes

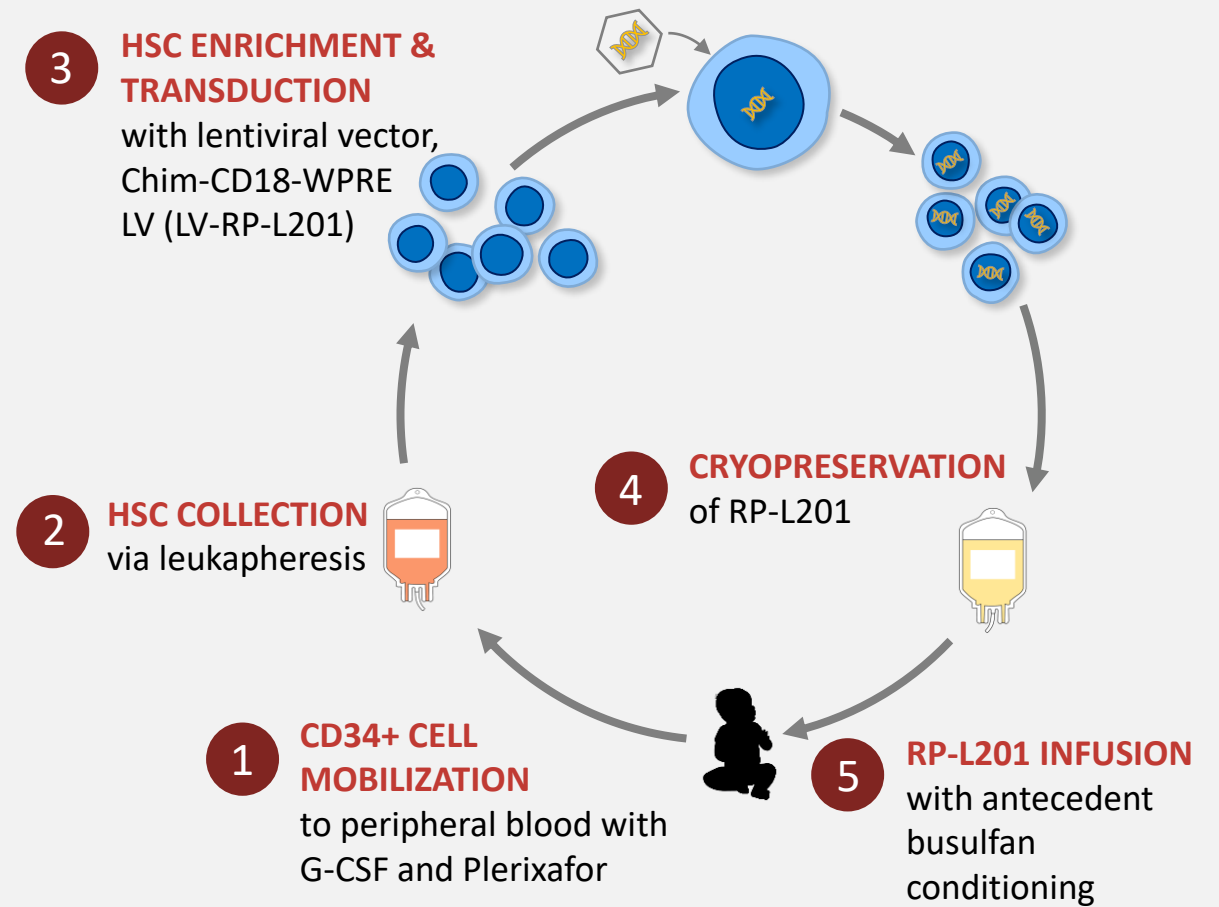
Almaraz E et al. J Allergy Clin Immunol Pract. 2018 July-August (6) 1418-1420.

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 β 2-integrin receptor family.



Developed at CIEMAT, in partnership with UCL



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 or fungal infection

Primary Outcomes

Phase 1:

- Safety & preliminary efficacy

Phase 2:

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

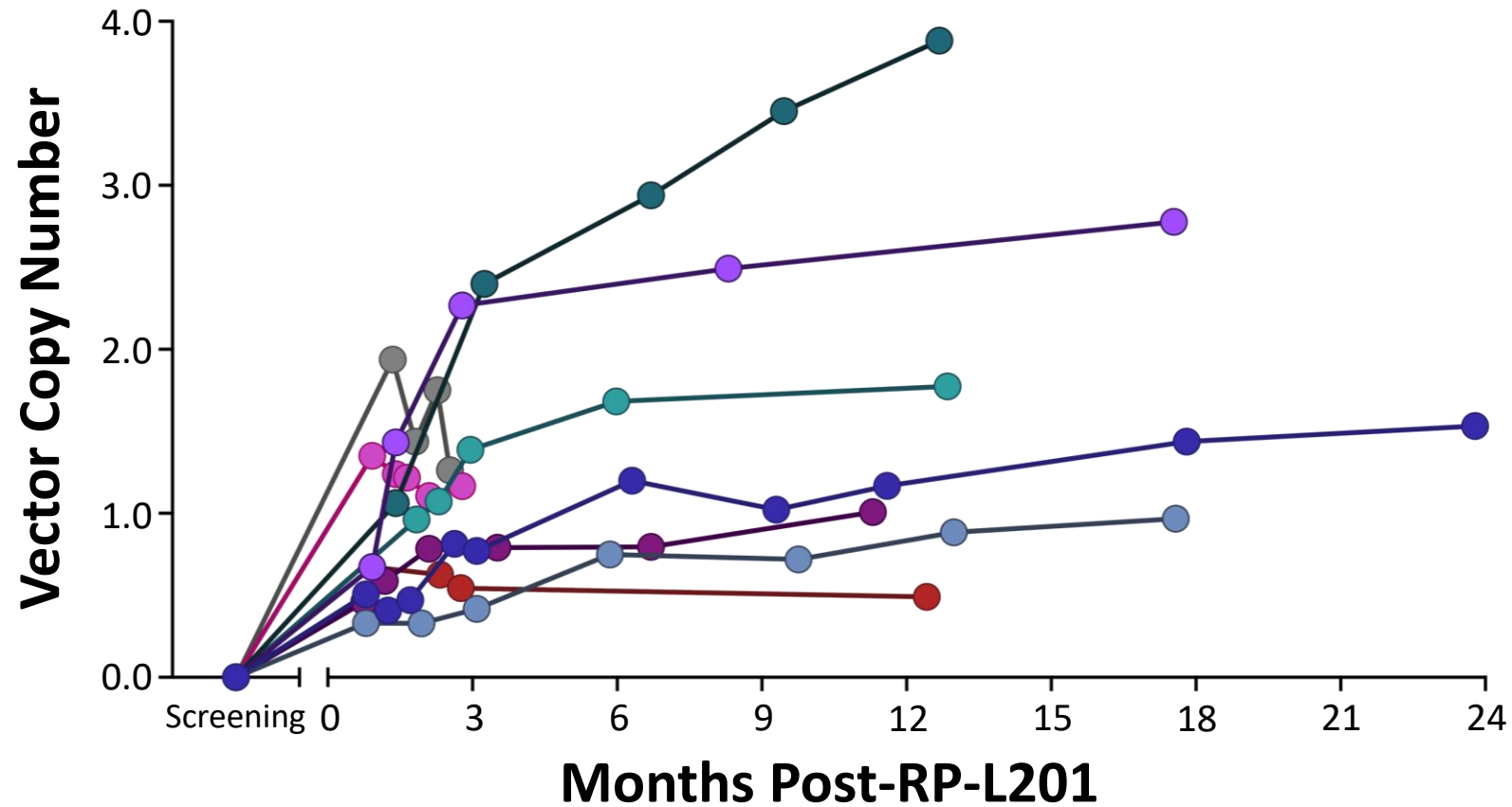
Secondary Outcomes

- **Incidence and severity of infections** (e.g., incidence of severe infections, hospitalizations and prolonged hospitalizations)
- % of pts **w/neutrophil CD18 expression at least 10% of normal**
- % of pts w/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
L201-003-2011	F	2 years	3.8	3.8×10^6 cells/kg
L201-002-2010	F	4 years	3.5	10×10^6 cells/kg

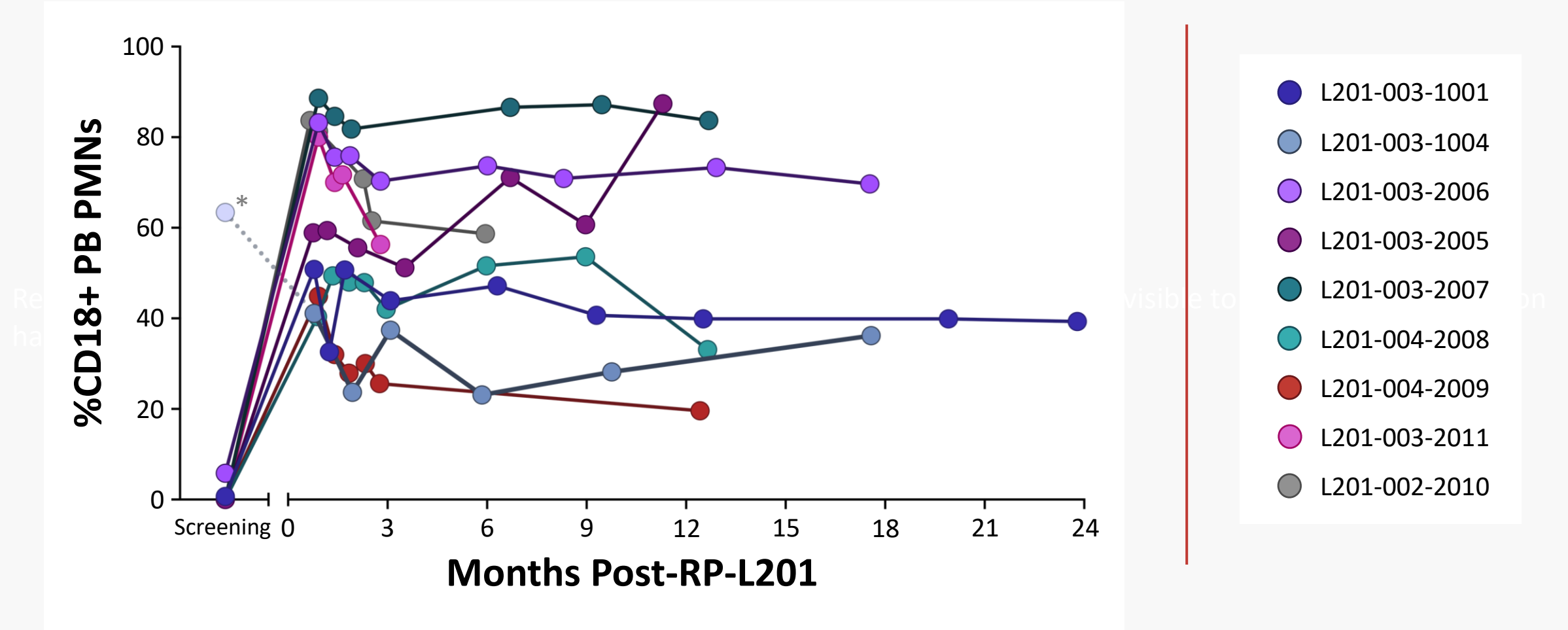
As of March 9, 2022: Data reported from 9 of 9 patients (3–24m follow-up). **Study enrollment is completed. All subjects have been treated.**

VCN in Peripheral Blood Mononuclear Cells



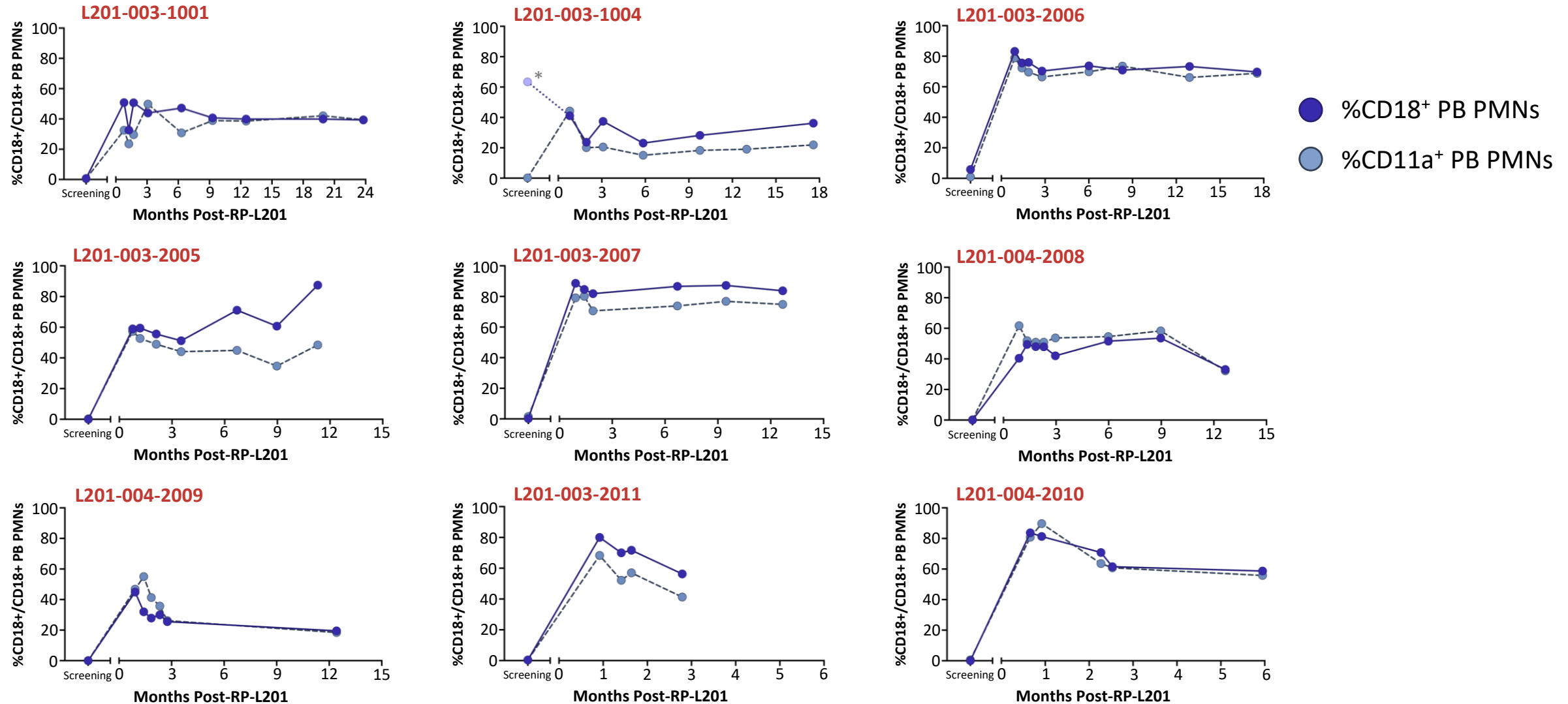
- L201-003-1001
- L201-003-1004
- L201-003-2006
- L201-003-2005
- L201-003-2007
- L201-004-2008
- L201-004-2009
- L201-003-2011
- L201-002-2010

CD18+ Expression in PB Polymorphonuclear Cells (PMNs)



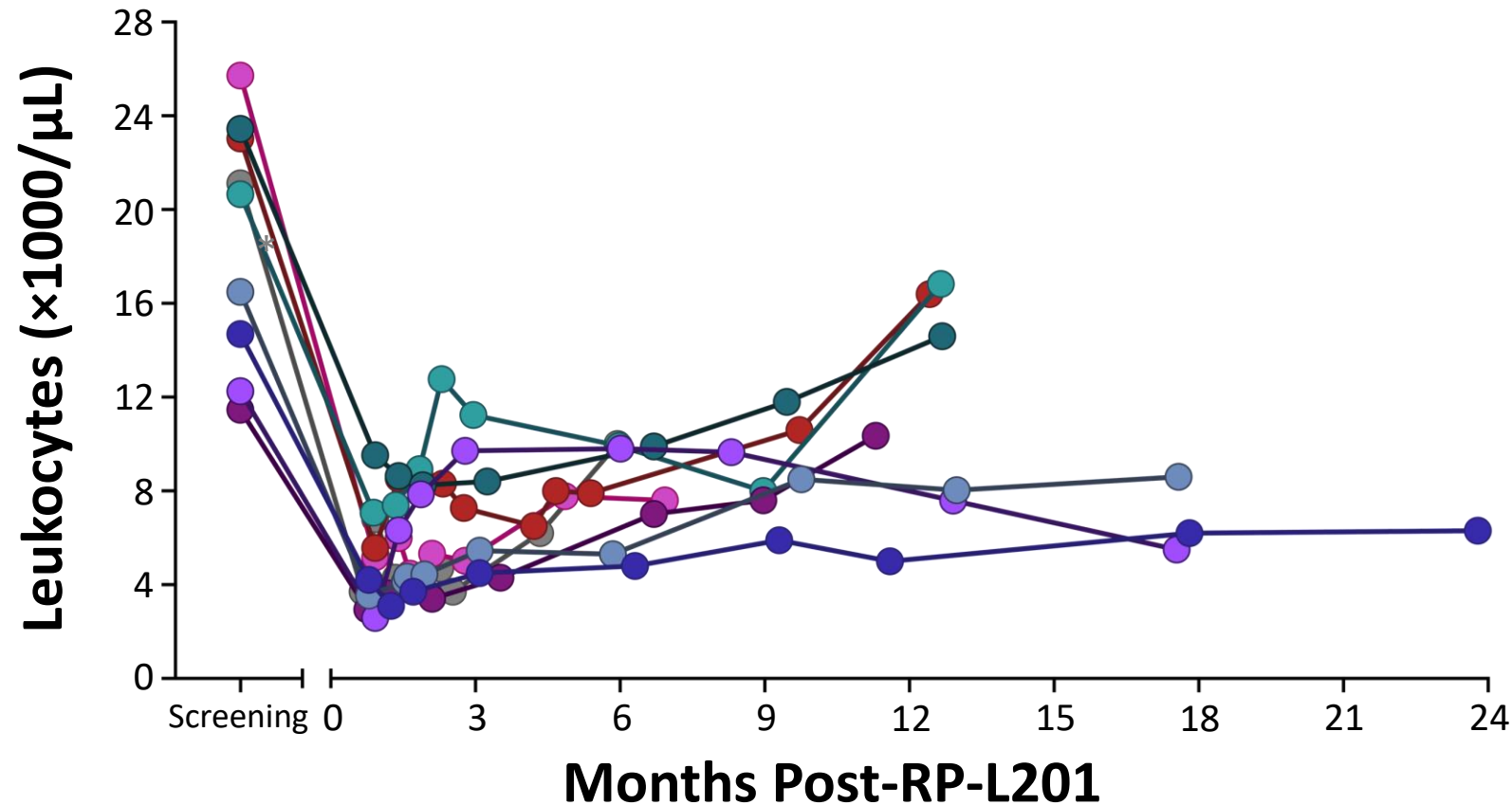
* Dim/weak CD18+ expression reported at baseline for Subject L201-003-1004 in ~63% of cells in conjunction with <2% CD11a/CD11b expression, likely indicating abnormal/unstable protein

CD18+ and CD11a+ Expression in PB PMNs



* Dim/weak CD18⁺ expression reported at baseline for Subject L201-003-1004 in ~63% of cells

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

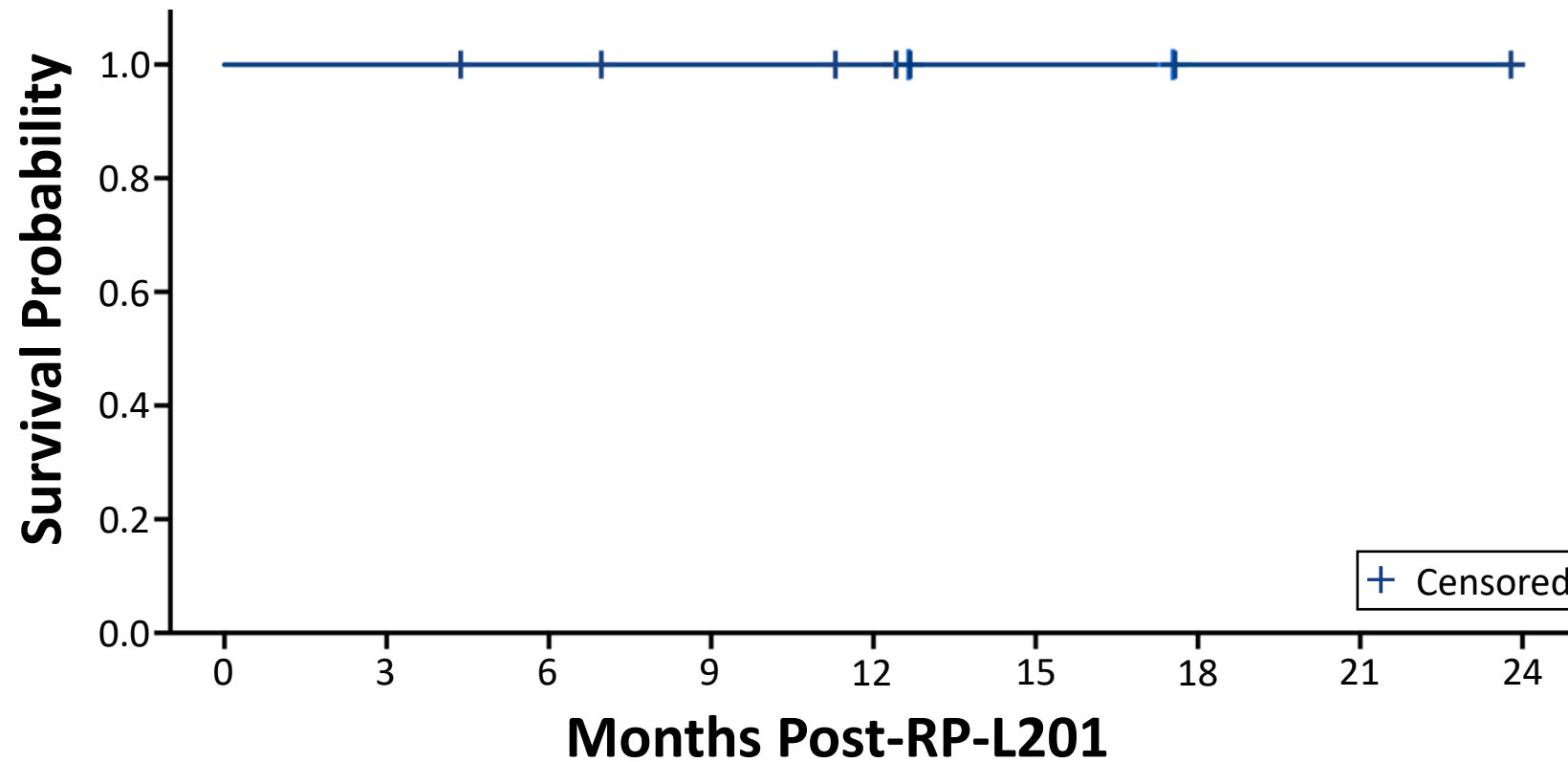


- Age at Enrollment
- L201-003-1001 (9y)
 - L201-003-1004 (3y)
 - L201-003-2006 (7mo)
 - L201-003-2005 (3y)
 - L201-003-2007 (3mo)
 - L201-004-2008 (5mo)
 - L201-004-2009 (3y)
 - L201-003-2011 (2y)
 - L201-002-2010 (4y)

Normal Leukocyte Ranges per Age Group: 0 months to <3 months: $7.20\text{--}18.00 \times 1000/\mu\text{L}$; ≥ 3 months to <6 months: $6.70\text{--}14.00 \times 1000/\mu\text{L}$; ≥ 6 months to 12 months: $6.40\text{--}13.00 \times 1000/\mu\text{L}$; 12 months to <2 years: $6.40\text{--}12.00 \times 1000/\mu\text{L}$; ≥ 2 to <6 years: $5.20\text{--}11.00 \times 1000/\mu\text{L}$; ≥ 6 years to <12 years: $4.40\text{--}9.50 \times 1000/\mu\text{L}$; ≥ 12 years to <18 years: $4.40\text{--}8.10 \times 1000/\mu\text{L}$

Overall Survival

Overall Survival (OS) Kaplan-Meier Estimate



**Survival without
allogeneic HSCT**

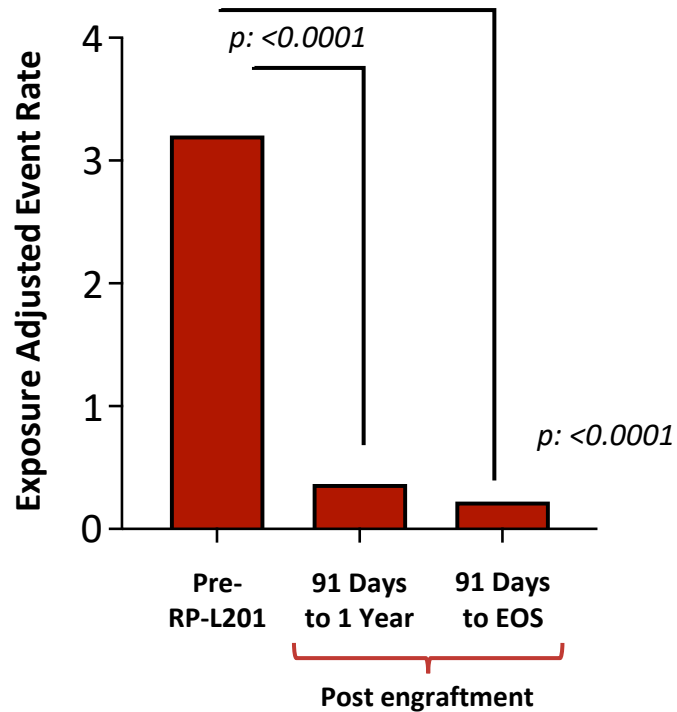
Primary Outcomes

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

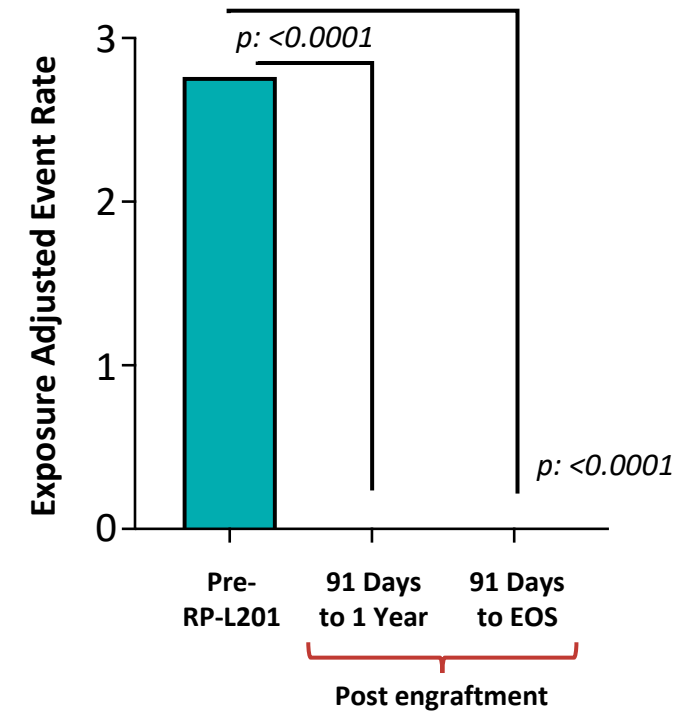
RP-L201 Clinical Outcome Measures

Incidence of All Hospitalizations and Infection and Inflammatory Related Hospitalizations

Incidence of Hospitalizations



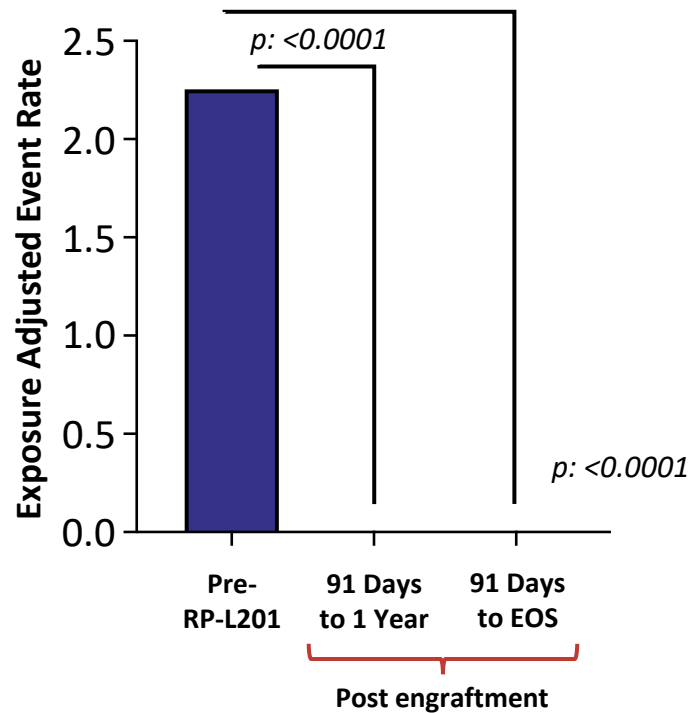
Incidence of Infection and Inflammatory Related Hospitalizations



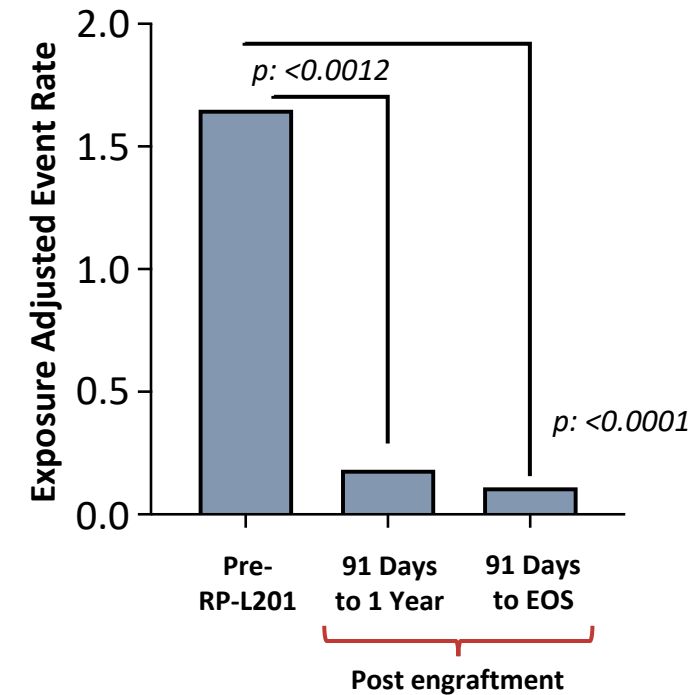
RP-L201 Clinical Outcome Measures

Incidence of Prolonged Hospitalizations and Severe Infections

Incidence of Prolonged (>7 days) Infection and Inflammatory Related Hospitalization



Incidence of Severe Infections



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

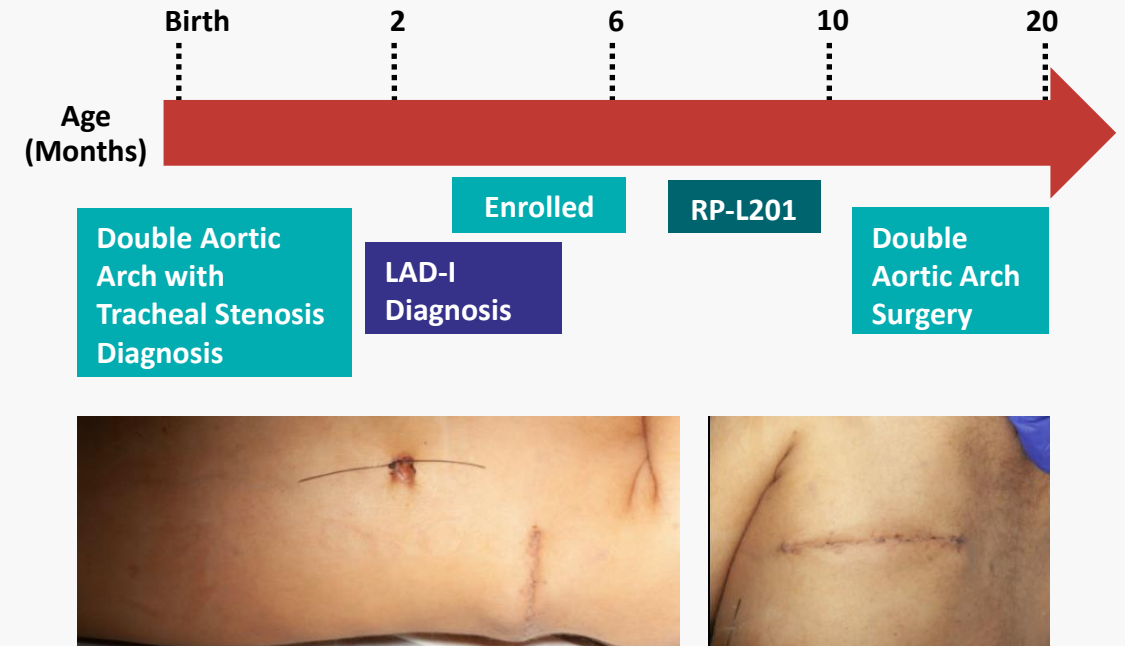
Spontaneous resolution of abdominal lesion

L201-003-1001



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

L201-004-2008



Clinical Safety Overview

As of March 9, 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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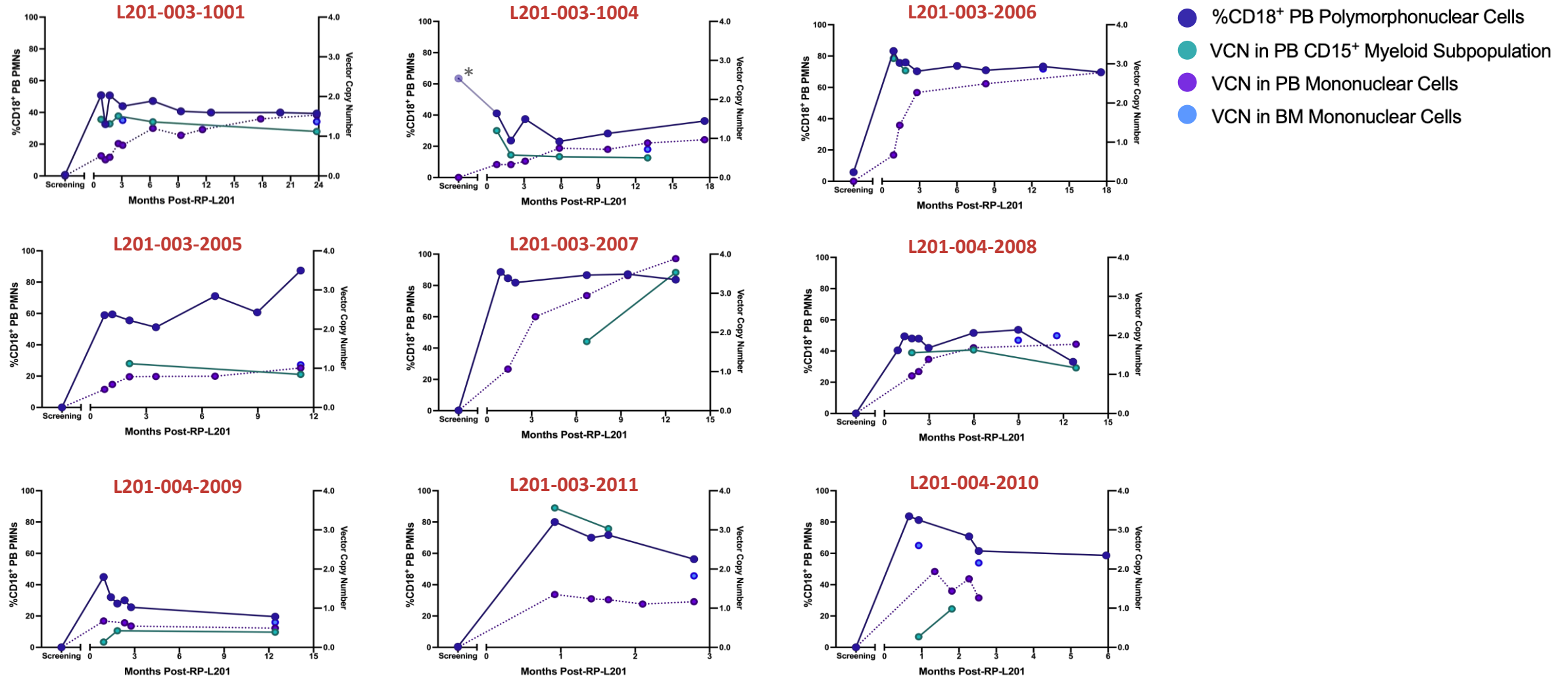


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Appendix

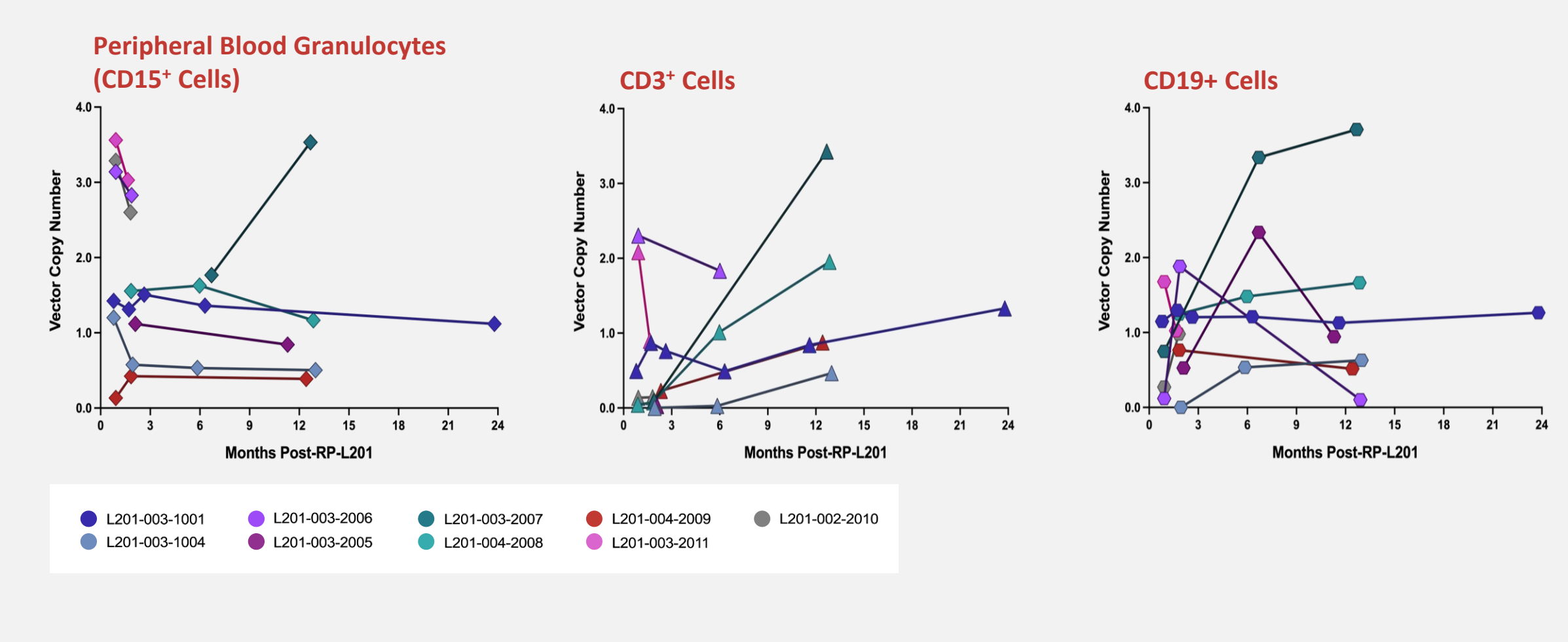
Interim Results: A Phase 1/2 Study of Lentiviral-Mediated Ex-Vivo Gene Therapy for Pediatric Patients with Severe Leukocyte Adhesion Deficiency-I (LAD-I)

CD18+ Expression and Vector Copy Number in PB and BM

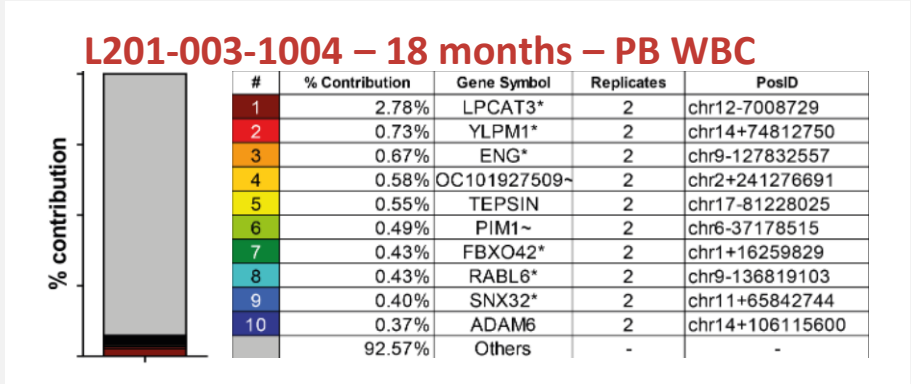
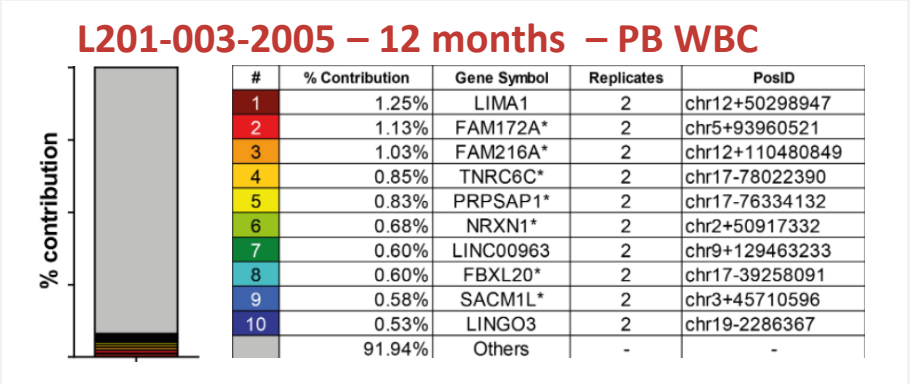
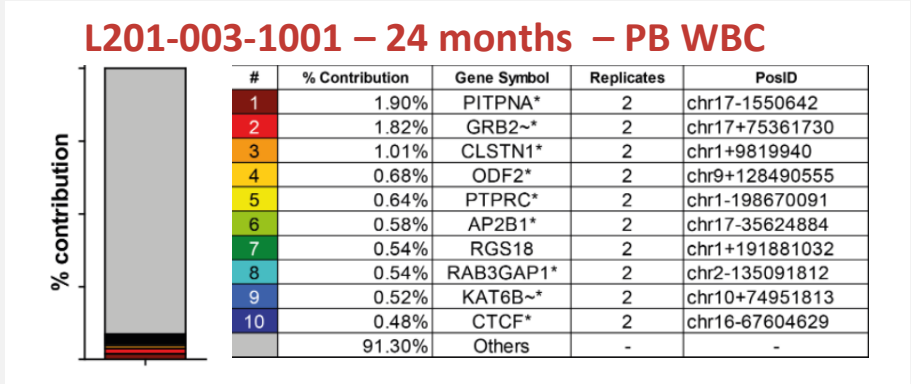


*Dim/weak CD18⁺ expression reported at baseline for Subject L201-003-1004 in ~63% of cells

Efficacy as Demonstrated by VCN in Peripheral Blood Subpopulations

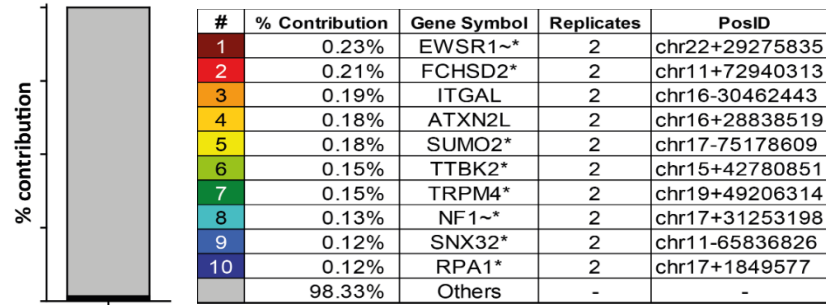


Integration Site Analysis (ISA) – Top 10 Integration Sites

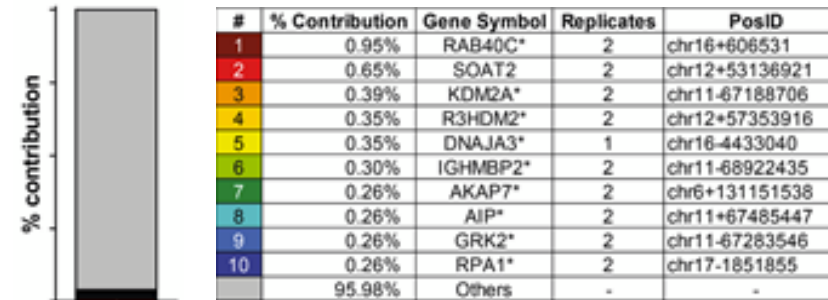


Integration Site Analysis (ISA) – Top 10 Integration Sites

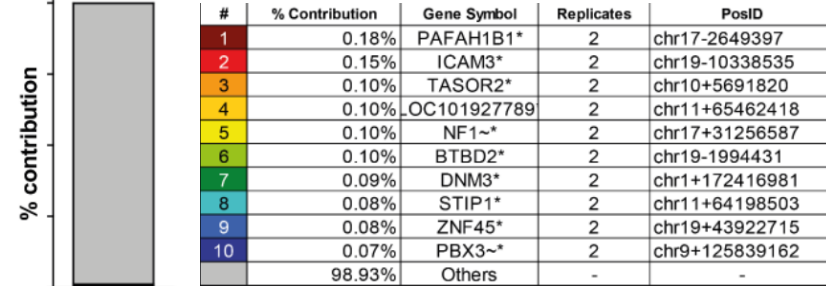
L201-003-2006 – 9 months – PB WBC



L201-004-2009 – 3 months – PB WBC

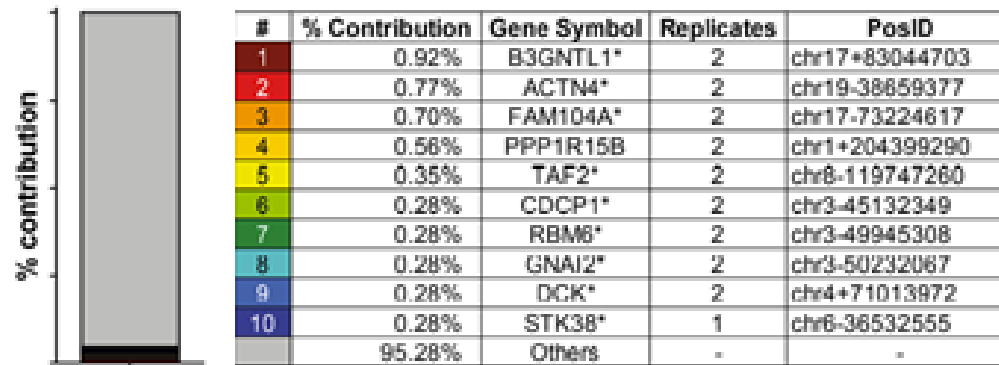


L201-003-2007 – 6 months – PB WBC



Integration Site Analysis (ISA) – Top 10 Integration Sites

L201-004-2008 – 3 months – PB WBC



L201-003-2011 – 3 months – BM WBC

