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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Abstract # INV20

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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

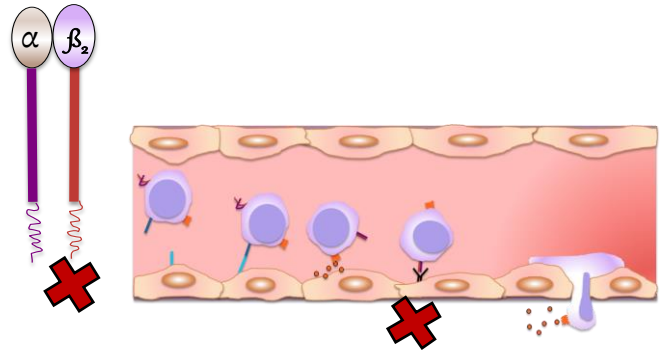
- Mutations affect the common chain (CD18) of the beta2-integrin family (*ITGB2* gene) and prevent functional CD18/CD11 heterodimer expression on leukocyte cell surfaces – essential for cell adhesion and subsequent migration.
- Severe LAD-I is characterized by recurrent and ultimately fatal disseminated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

LAD-I Disease Spectrum

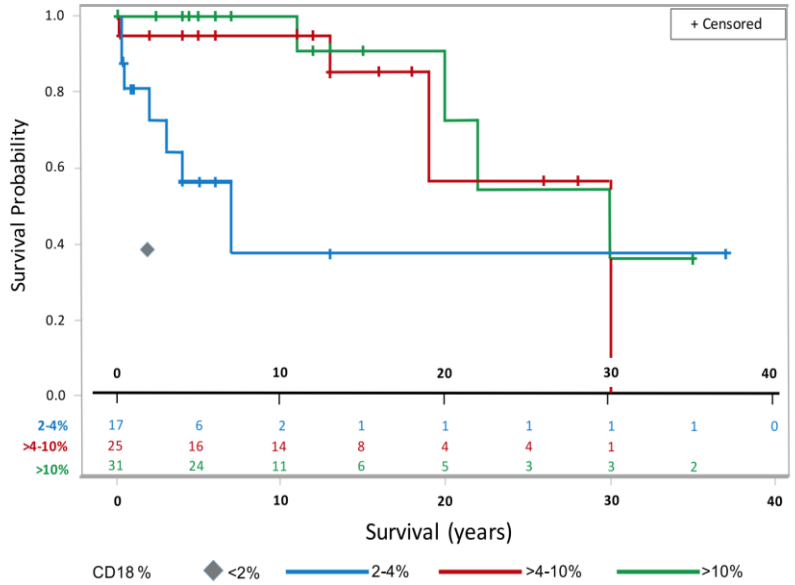
Moderate: 2–30% CD18+ PMN ⟷ Severe: <2% CD18+ PMN

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

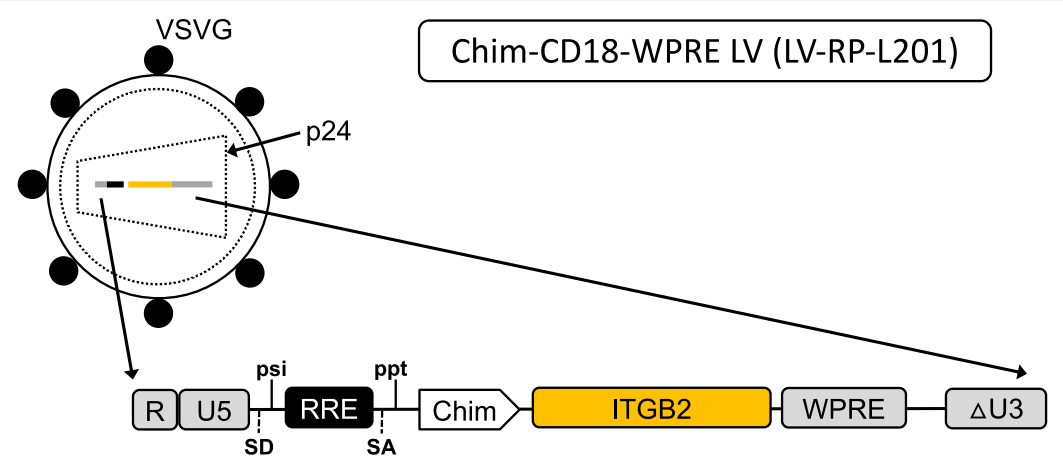
◆: **39% survival to age 2 years** for 66 evaluable patients with severe LAD-I not receiving HSCT

HSCT: hematopoietic stem cell transplantation; PMN: polymorphonuclear leukocytes

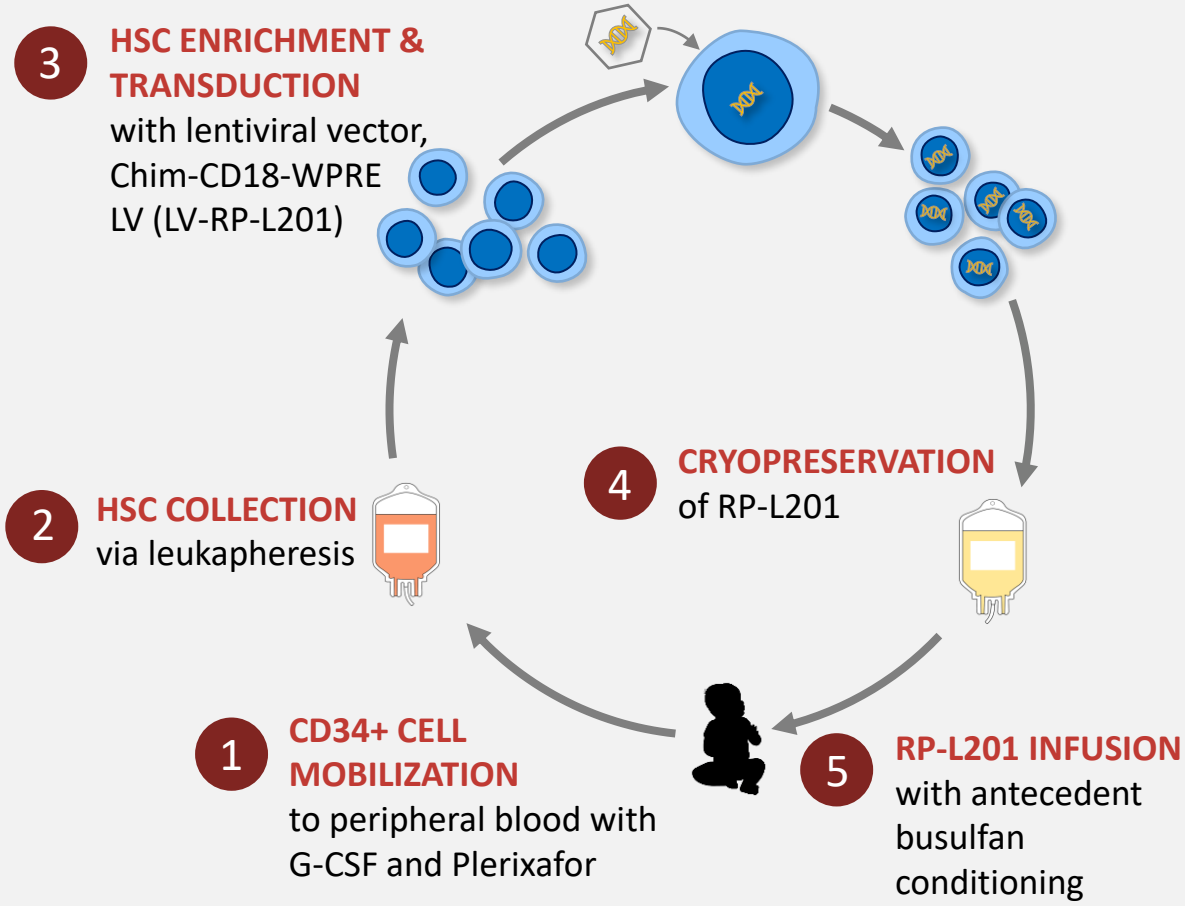
Almarza E et al. J Allergy Clin Immunol Pract. 2018 July-August (6) 1418-1420.

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



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

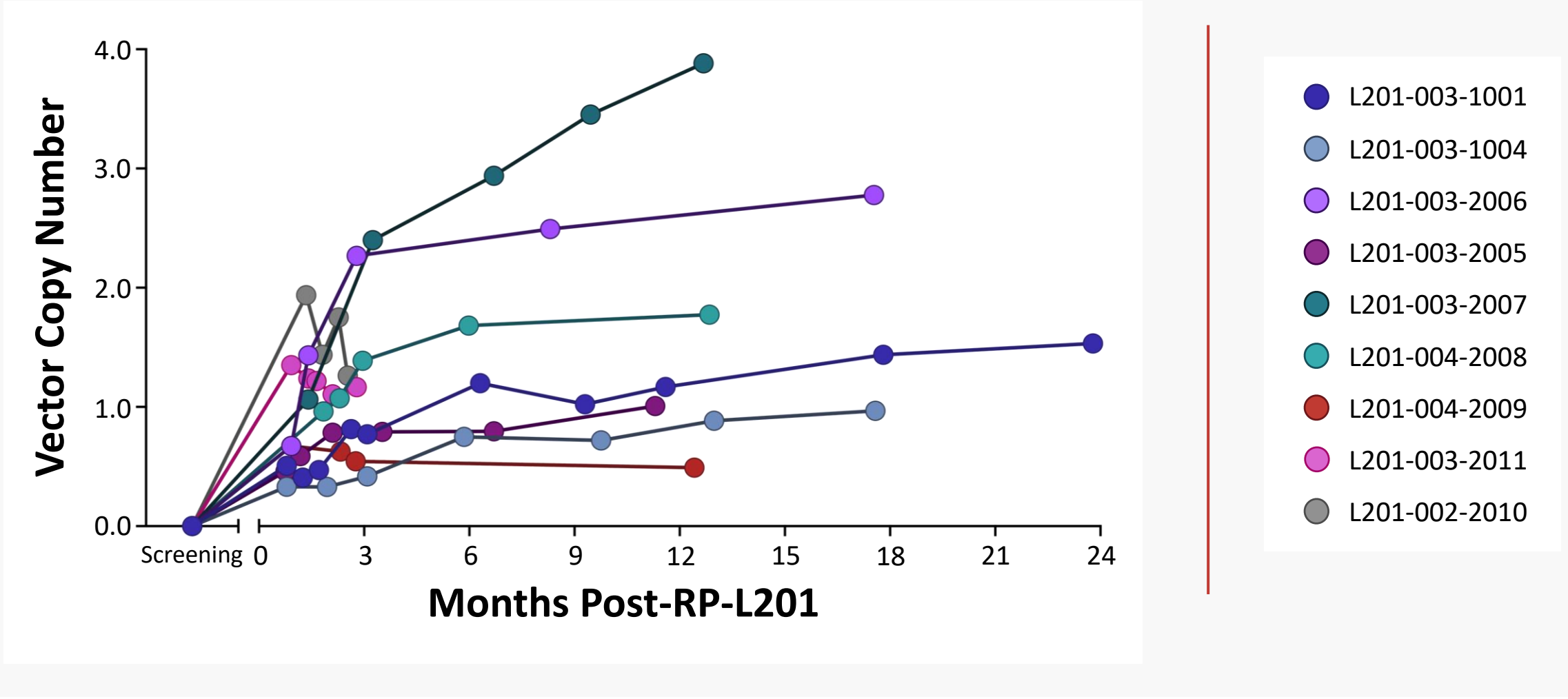
Secondary Outcomes

- **Incidence and severity of infections** (e.g., incidence of severe infections, hospitalizations and prolonged hospitalizations)
- % of 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**

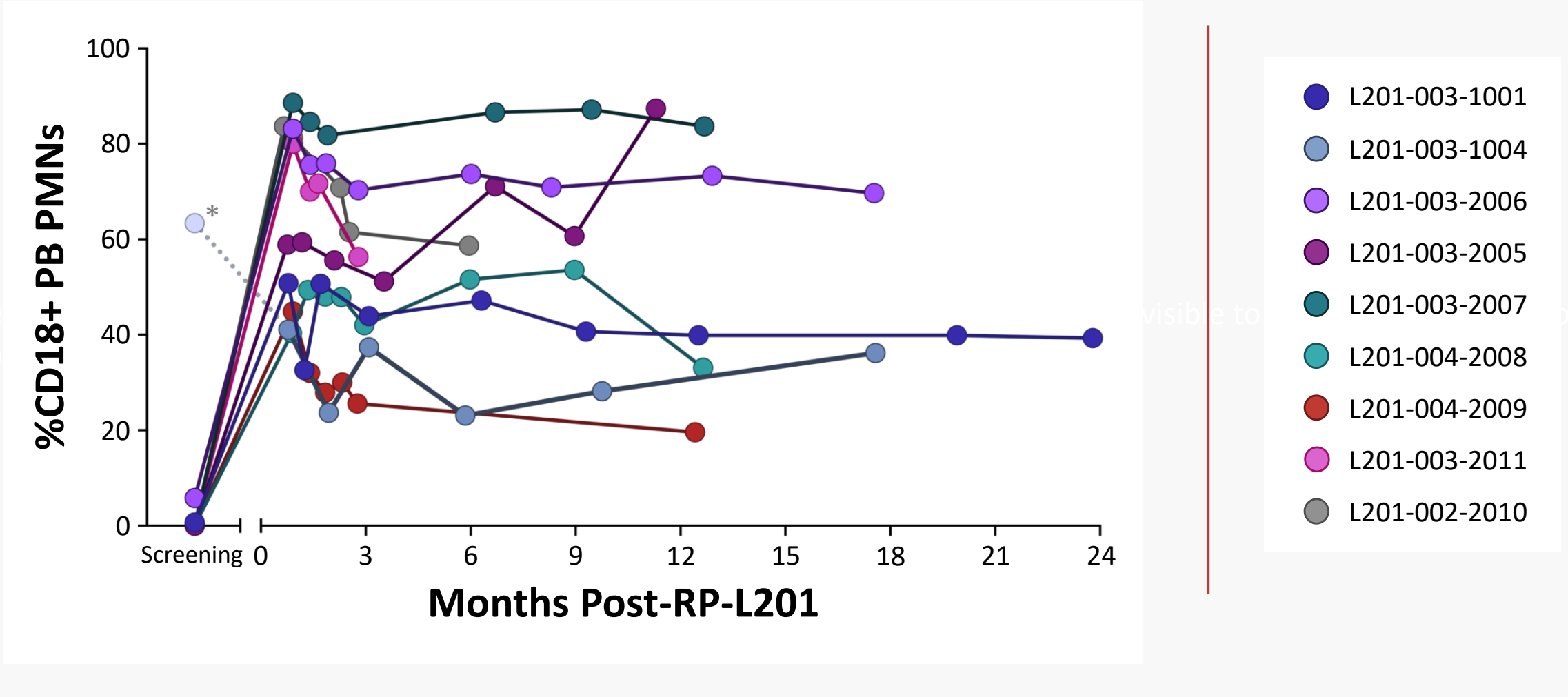
Patient	Sex	Age at enrollment	Drug Product VCN	CD34+ Cell Dose
L201-003-1001	F	9 years	3.8	4.2×10^6 cells/kg
L201-003-1004	F	3 years	2.5	2.8×10^6 cells/kg
L201-003-2005	F	3 years	1.8	6.5×10^6 cells/kg
L201-003-2006	M	7 months	2.9	4.3×10^6 cells/kg
L201-003-2007	M	3 months	3.6	5.0×10^6 cells/kg
L201-004-2008	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
L201-002-2010	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 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 (PBMCs)

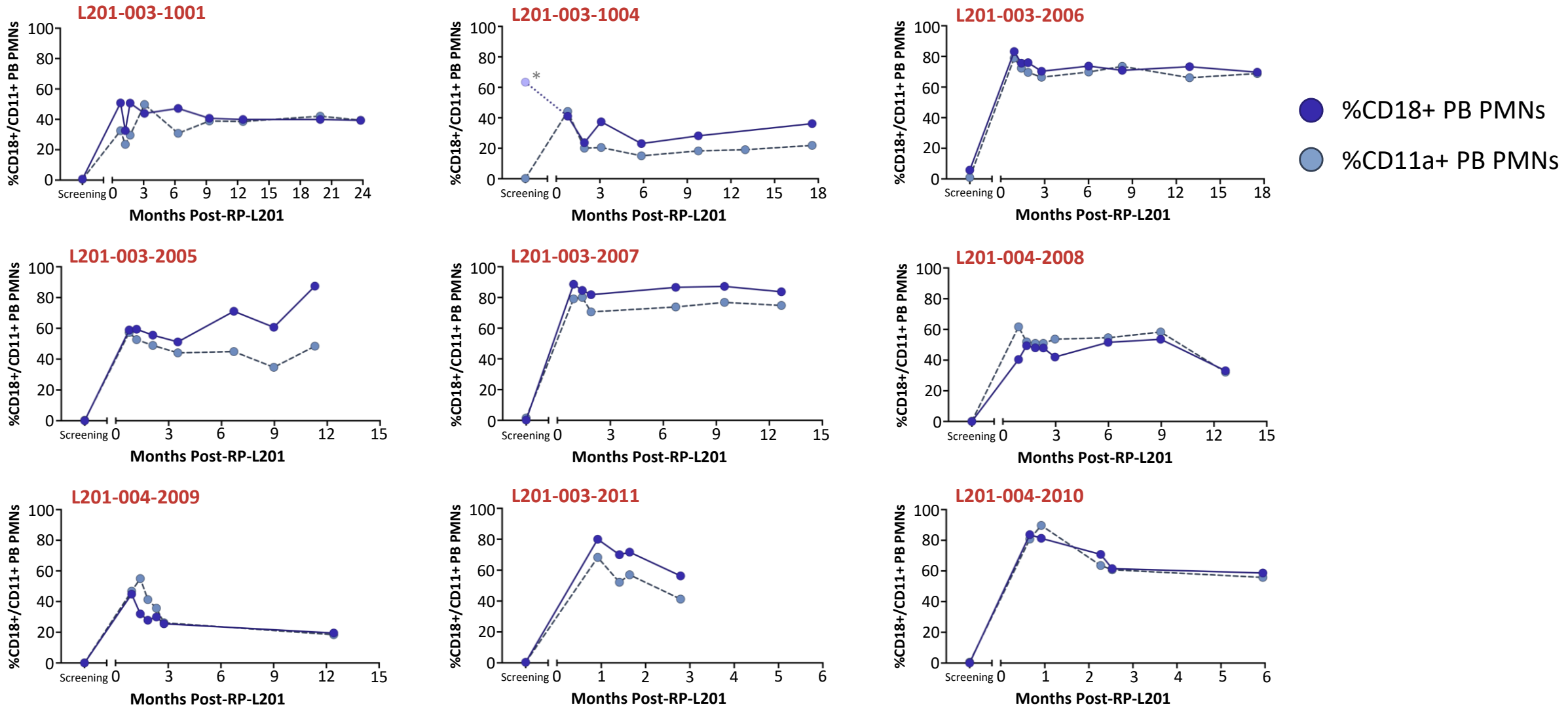


CD18 Expression in PB Polymorphonuclear Cells (PMNs)



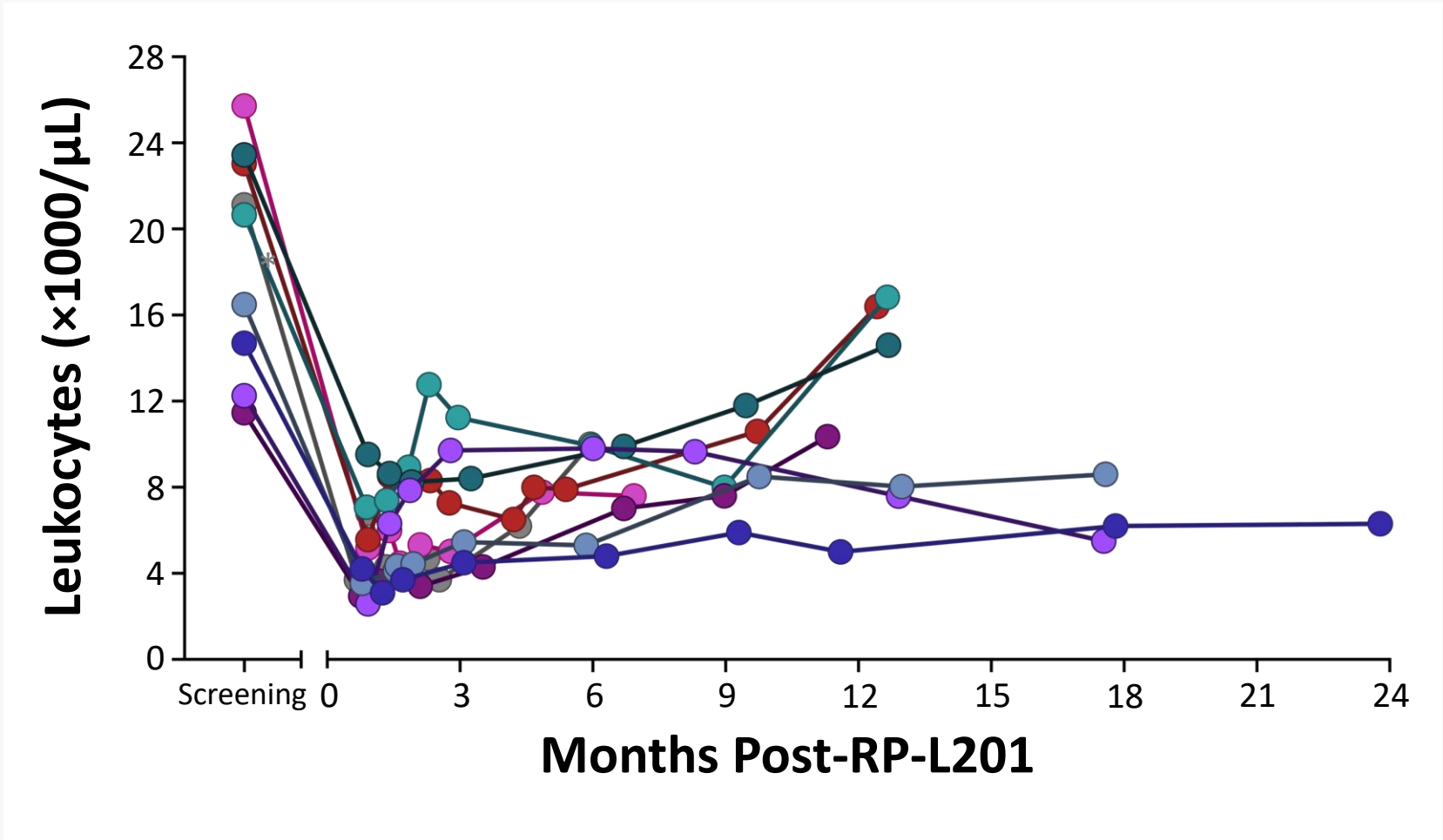
* Dim/weak CD18 expression reported at baseline for Subject L201-003-1004 in ~63% of cells in conjunction with <2% CD11a/CD11b expression, likely indicating abnormal/unstable protein

CD18 and CD11a Expression in PB PMNs



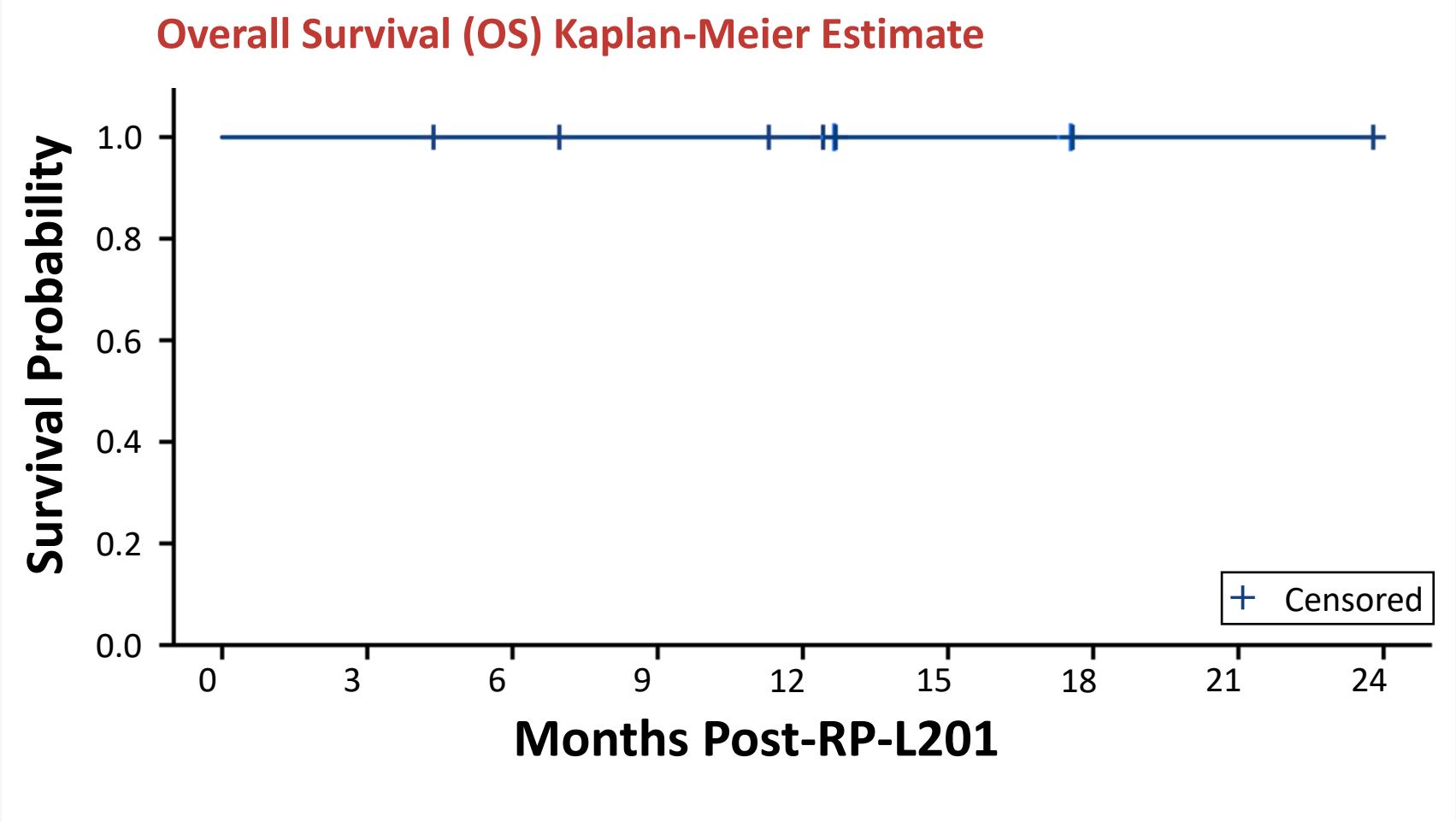
* Dim/weak CD18 expression reported at baseline for Subject L201-003-1004 in ~63% of cells in conjunction with <2% CD11a/CD11b expression, likely indicating abnormal/unstable protein

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



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*

Overall Survival



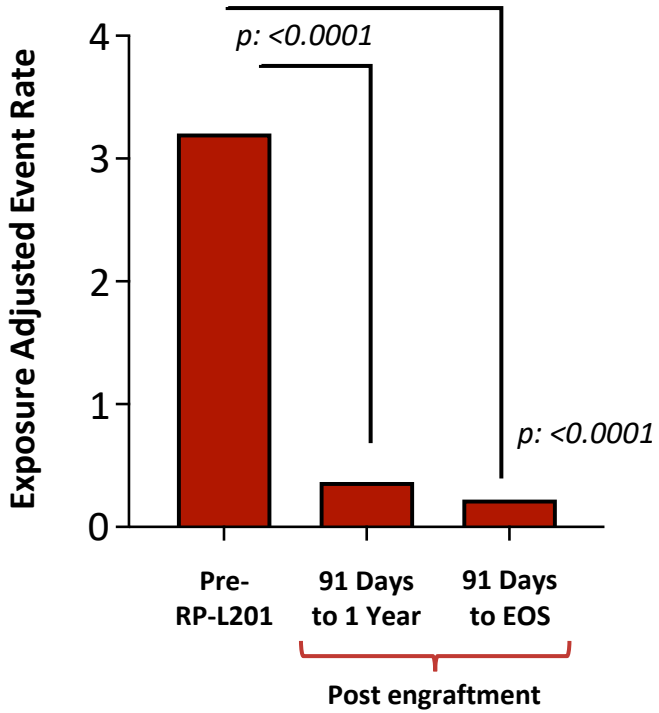
Survival without allogeneic HSCT

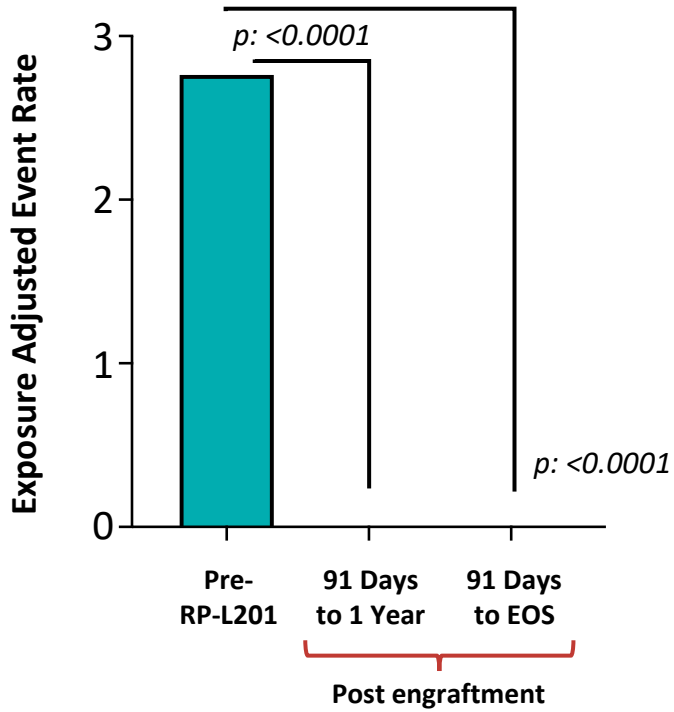
Primary Outcomes

- >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



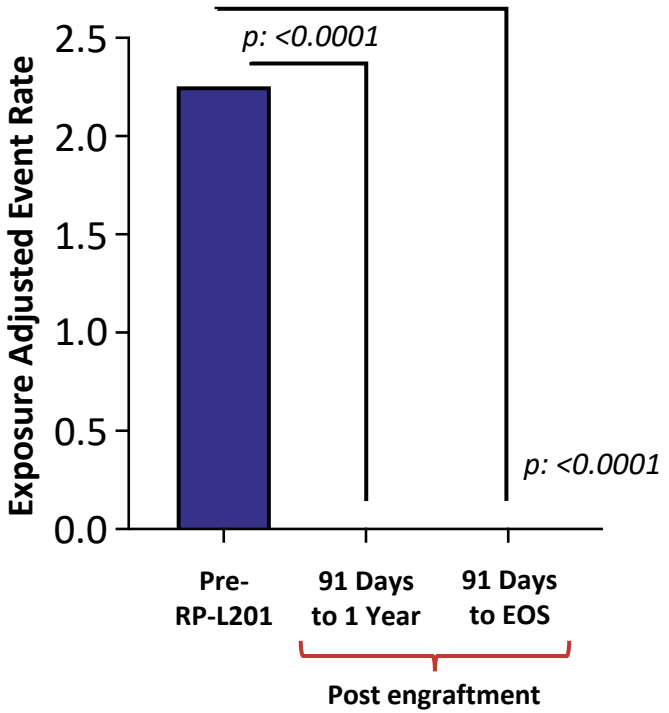


EOS: end of study

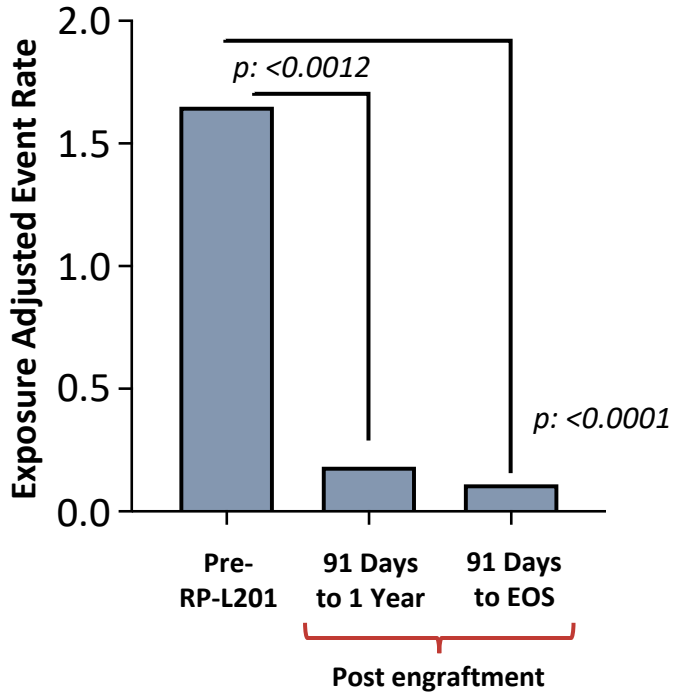
RP-L201 Clinical Outcome Measures

Incidence of Prolonged Hospitalizations and Severe Infections

Incidence of Prolonged (>7 days) Hospitalization



Incidence of Severe Infections



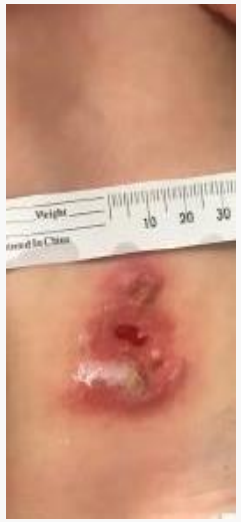
EOS: end of study

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

Spontaneous resolution of abdominal lesion

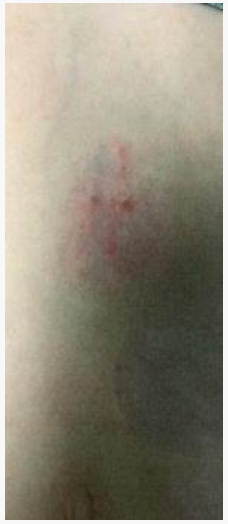
L201-003-1001

Baseline



3 months Post-RP-L201

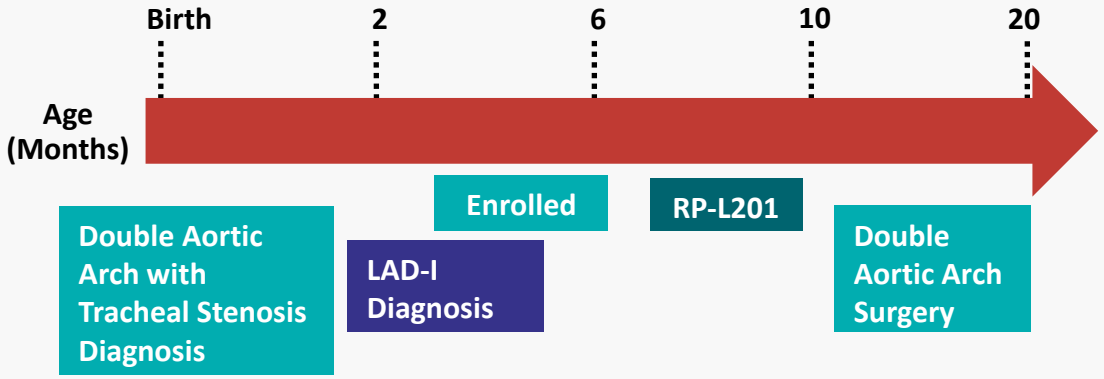
6 months Post-RP-L201

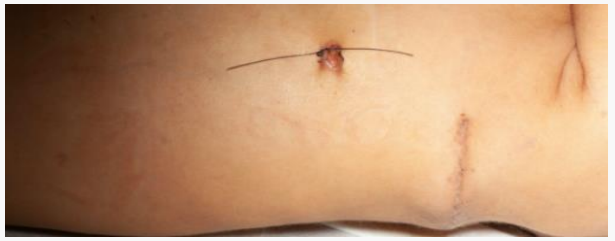


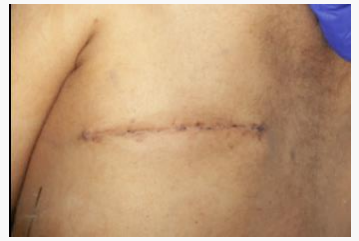
12 months Post-RP-L201

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

L201-004-2008







Clinical Safety Overview

As of 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 m 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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Appendix

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)

25TH ASGCT
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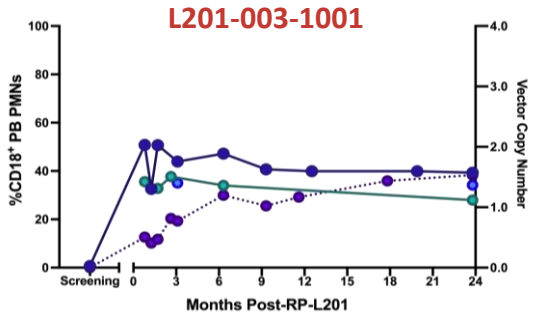
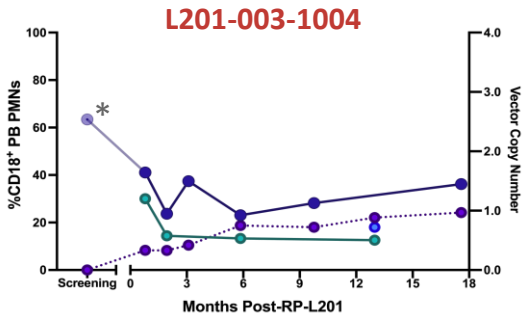
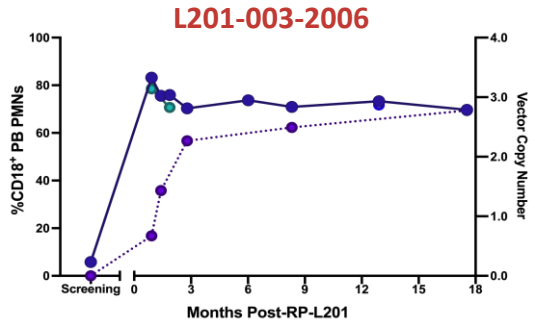
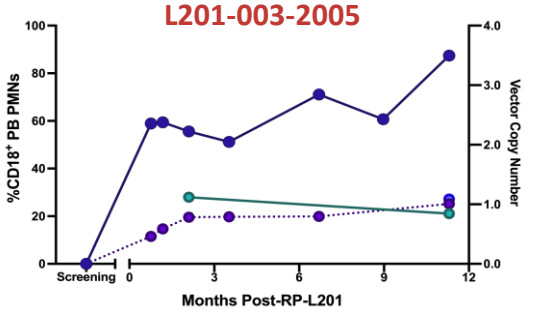
Children's Discovery & Innovation Institute

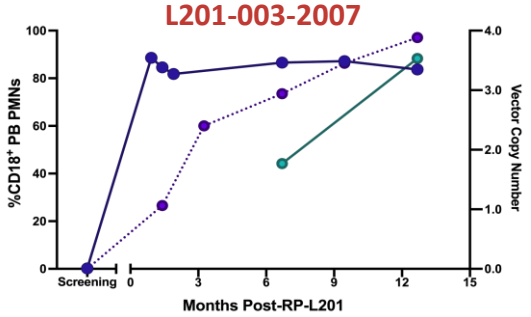
CD18 Expression and Vector Copy Number in PB and BM

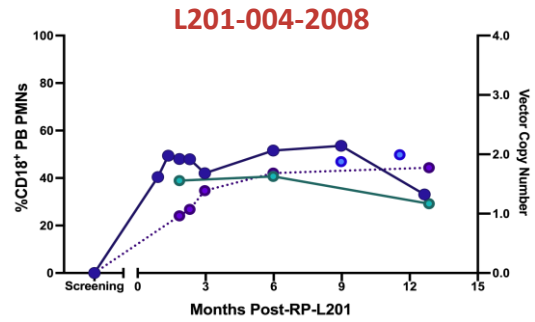


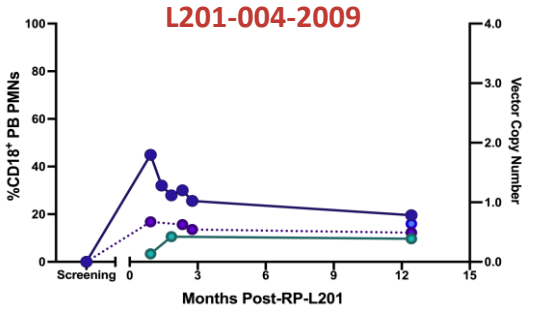


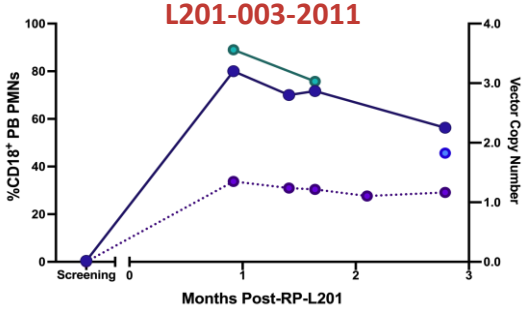


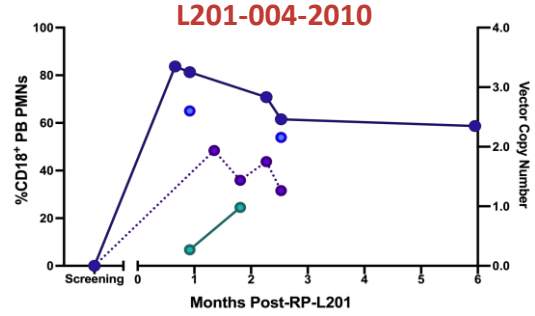








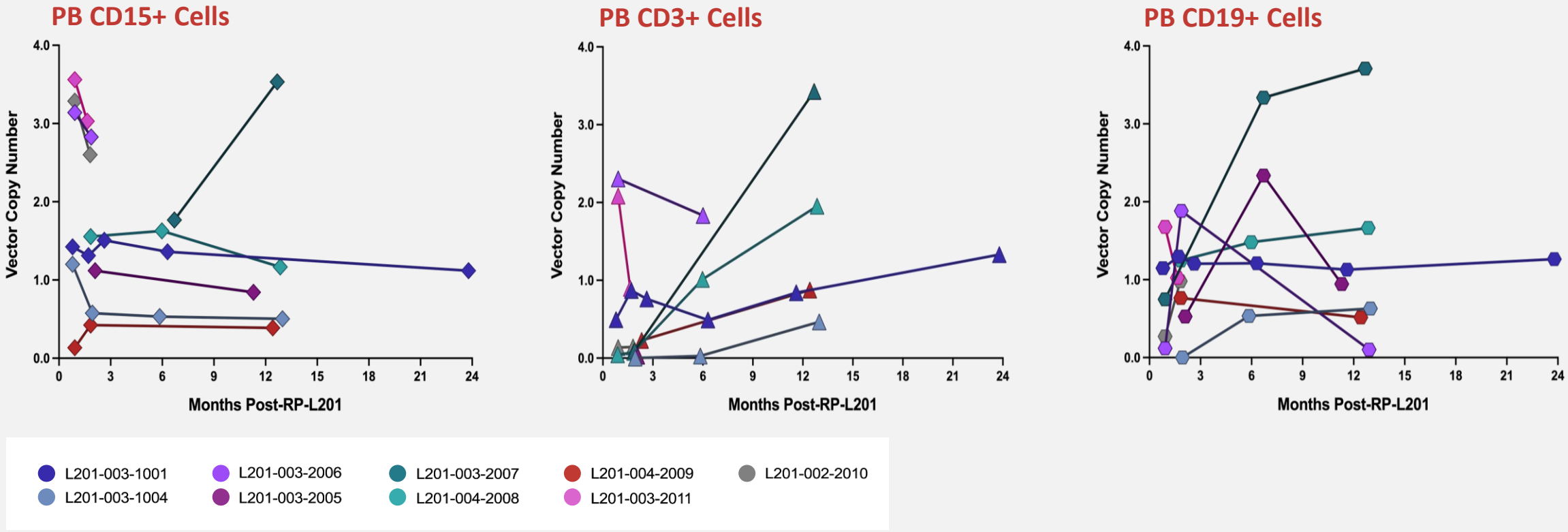




- %CD18+ PB Polymorphonuclear Cells
- VCN in PB CD15+ Myeloid Subpopulation
- VCN in PB Mononuclear Cells
- VCN in BM Mononuclear Cells

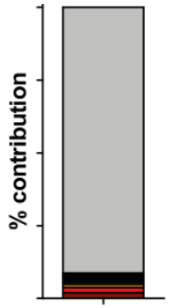
*Dim/weak CD18+ expression reported at baseline for Subject L201-003-1004 in ~63% of cells

Efficacy as Demonstrated by VCN in Peripheral Blood Subpopulations



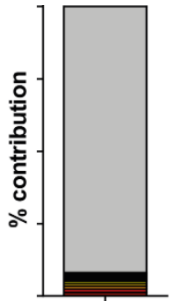
Integration Site Analysis (ISA) – Top 10 Integration Sites

L201-003-1001 – 24 months – PB WBC



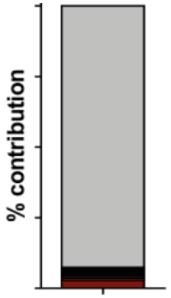
#	% Contribution	Gene Symbol	Replicates	PosID
1	1.90%	PITPNA*	2	chr17-1550642
2	1.82%	GRB2~*	2	chr17+75361730
3	1.01%	CLSTN1*	2	chr1+9819940
4	0.68%	ODF2*	2	chr9+128490555
5	0.64%	PTPRC*	2	chr1-198670091
6	0.58%	AP2B1*	2	chr17-35624884
7	0.54%	RGS18	2	chr1+191881032
8	0.54%	RAB3GAP1*	2	chr2-135091812
9	0.52%	KAT6B~*	2	chr10+74951813
10	0.48%	CTCF*	2	chr16-67604629
	91.30%	Others	-	-

L201-003-2005 – 12 months – PB WBC



#	% Contribution	Gene Symbol	Replicates	PosID
1	1.25%	LIMA1	2	chr12+50298947
2	1.13%	FAM172A*	2	chr5+93960521
3	1.03%	FAM216A*	2	chr12+110480849
4	0.85%	TNRC6C*	2	chr17-78022390
5	0.83%	PRPSAP1*	2	chr17-76334132
6	0.68%	NRXN1*	2	chr2+50917332
7	0.60%	LINC00963	2	chr9+129463233
8	0.60%	FBXL20*	2	chr17-39258091
9	0.58%	SACM1L*	2	chr3+45710596
10	0.53%	LINGO3	2	chr19-2286367
	91.94%	Others	-	-

L201-003-1004 – 18 months – PB WBC

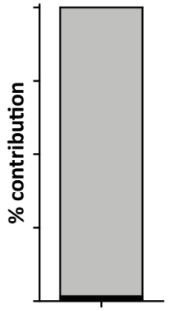


#	% Contribution	Gene Symbol	Replicates	PosID
1	2.78%	LPCAT3*	2	chr12-7008729
2	0.73%	YLPM1*	2	chr14+74812750
3	0.67%	ENG*	2	chr9-127832557
4	0.58%	OC101927509~	2	chr2+241276691
5	0.55%	TEPSIN	2	chr17-81228025
6	0.49%	PIM1~	2	chr6-37178515
7	0.43%	FBXO42*	2	chr1+16259829
8	0.43%	RABL6*	2	chr9-136819103
9	0.40%	SNX32*	2	chr11+65842744
10	0.37%	ADAM6	2	chr14+106115600
	92.57%	Others	-	-

PB WBC: White Blood Cells in Peripheral Blood

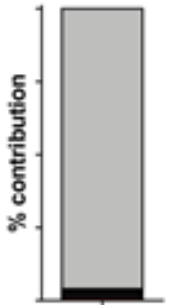
Integration Site Analysis (ISA) – Top 10 Integration Sites

L201-003-2006 – 9 months – PB WBC



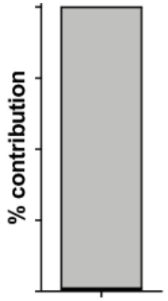
#	% Contribution	Gene Symbol	Replicates	PosID
1	0.23%	EWSR1~*	2	chr22+29275835
2	0.21%	FCHSD2*	2	chr11+72940313
3	0.19%	ITGAL	2	chr16-30462443
4	0.18%	ATXN2L	2	chr16+28838519
5	0.18%	SUMO2*	2	chr17-75178609
6	0.15%	TTBK2*	2	chr15+42780851
7	0.15%	TRPM4*	2	chr19+49206314
8	0.13%	NF1~*	2	chr17+31253198
9	0.12%	SNX32*	2	chr11-65836826
10	0.12%	RPA1*	2	chr17+1849577
	98.33%	Others	-	-

L201-004-2009 – 3 months – PB WBC



#	% Contribution	Gene Symbol	Replicates	PosID
1	0.95%	RAB40C*	2	chr16+606531
2	0.65%	SOAT2	2	chr12+53136921
3	0.39%	KDM2A*	2	chr11-67188706
4	0.35%	R3HDM2*	2	chr12+57353916
5	0.35%	DNAJA3*	1	chr16-4433040
6	0.30%	IGHMBP2*	2	chr11-68922435
7	0.26%	AKAP7*	2	chr6+131151538
8	0.26%	AIP*	2	chr11+67485447
9	0.26%	GRK2*	2	chr11-67283546
10	0.26%	RPA1*	2	chr17-1851855
	95.98%	Others	-	-

L201-003-2007 – 6 months – PB WBC

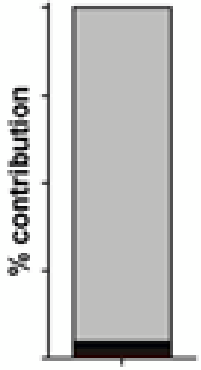


#	% Contribution	Gene Symbol	Replicates	PosID
1	0.18%	PAFAH1B1*	2	chr17-2649397
2	0.15%	ICAM3*	2	chr19-10338535
3	0.10%	TASOR2*	2	chr10+5691820
4	0.10%	OC101927789	2	chr11+65462418
5	0.10%	NF1~*	2	chr17+31256587
6	0.10%	BTBD2*	2	chr19-1994431
7	0.09%	DNM3*	2	chr1+172416981
8	0.08%	STIP1*	2	chr11+64198503
9	0.08%	ZNF45*	2	chr19+43922715
10	0.07%	PBX3~*	2	chr9+125839162
	98.93%	Others	-	-

PB WBC: White Blood Cells in Peripheral Blood

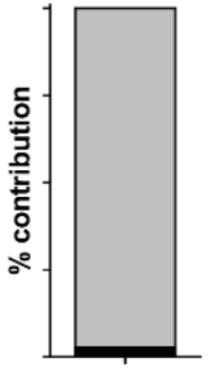
Integration Site Analysis (ISA) – Top 10 Integration Sites

L201-004-2008 – 3 months – PB WBC



#	% Contribution	Gene Symbol	Replicates	PosID
1	0.92%	B3GNTL1*	2	chr17+83044703
2	0.77%	ACTN4*	2	chr19-38659377
3	0.70%	FAM104A*	2	chr17-73224617
4	0.56%	PPP1R15B	2	chr1+204399290
5	0.35%	TAF2*	2	chr8-119747260
6	0.28%	CDCP1*	2	chr3-45132349
7	0.28%	RBM6*	2	chr3-49945308
8	0.28%	GNAI2*	2	chr3-50232067
9	0.28%	DCK*	2	chr4+71013972
10	0.28%	STK38*	1	chr6-36532555
	95.28%	Others	-	-

L201-003-2011 – 3 months – BM WBC



#	% Contribution	Gene Symbol	Replicates	PosID
1	0.33%	OMA1*	2	chr1-58509888
2	0.31%	GNA15*	2	chr19+3138668
3	0.29%	INO80*	2	chr15+41090663
4	0.29%	PPP6R2*	2	chr22+50382472
5	0.28%	SLC25A25*	2	chr9+128083015
6	0.28%	FCHSD2*	2	chr11-72968134
7	0.26%	DIP2A*	2	chr21-46471713
8	0.26%	RALY*	2	chr20-34032757
9	0.24%	EPS15~*	2	chr1+51429887
10	0.20%	ABCC1~*	2	chr16+16014027
	97.27%	Others	-	-

PB WBC: White Blood Cells in Peripheral Blood
BM WBC: White Blood Cells in Bone Marrow