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

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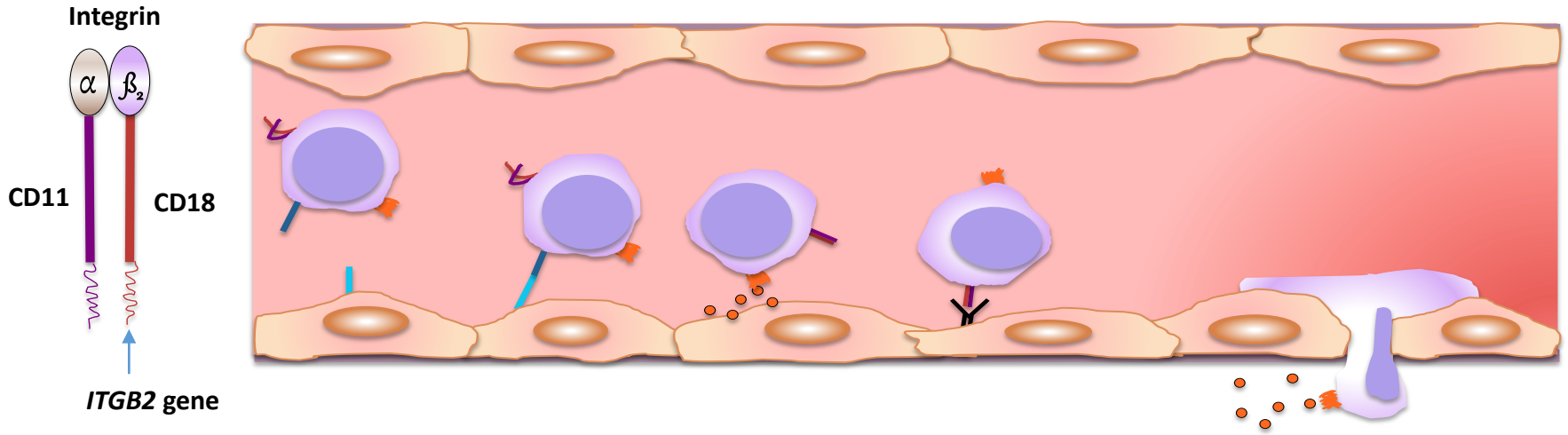
Mattel Children's Hospital UCLA
UCLA Children's Discovery and Innovation Institute

Conflict of Interest Statement – Dr. Kohn

I am a paid member of the Scientific Advisory Boards of
Orchard Therapeutics, Allogene Therapeutics, and MyoGene Bio

The UC Regents have licensed intellectual property on ADA SCID gene therapy on which I am an inventor to Orchard Therapeutics

Leukocyte Adhesion Deficiency-I (LAD-I)
Monogenic Immunodeficiency Disorder



- Mutations in the common chain (CD18) of the beta2-integrin family (*ITGB2* gene) prevent expression of CD18/CD11 heterodimers on cell surface essential for cell migration and adhesion
- LAD-I characterized by recurring and ultimately fatal infections due to inability of leukocytes to leave bloodstream and migrate to sites of tissue infection
- Severe inflammatory complications include omphalitis, gingivitis and ulcerative skin lesions
- Current Treatment Option: Allogeneic HSCT but frequently limited by availability of suitable donor, frequent & severe GvHD, infections.

Clinical Pathogenesis of LAD-I

LAD-I Disease Spectrum

Moderate:	Severe:
2-30%	<2%
CD18+ PMN	CD18+ PMN

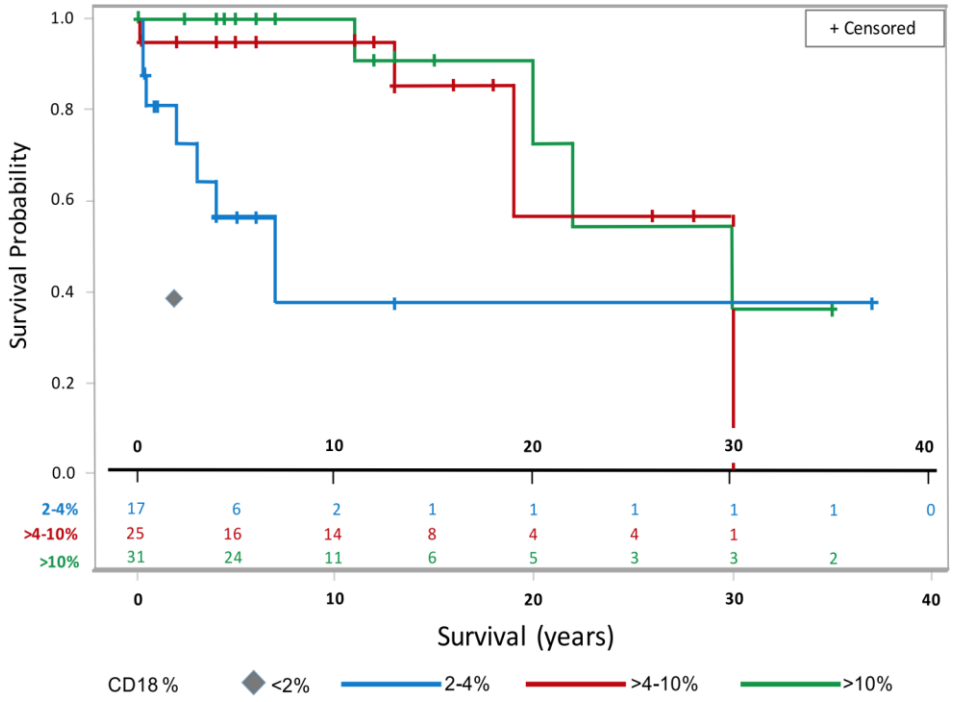
PMN = polymorphonuclear leukocytes

LAD-I Clinical Prognosis

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

Kaplan-Meier Survival Estimates by Neutrophil CD18 Expression

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

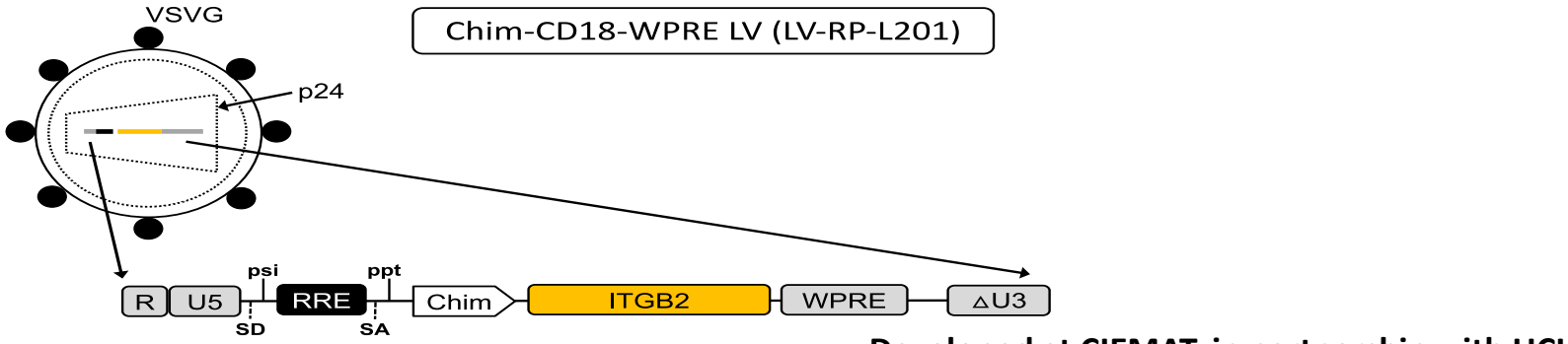


The grey diamond indicates the 39% survival to age 2 years for 66 evaluable patients with severe LAD-I not receiving HSCT

Almarza Novoa 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 for the CD18 (β-subunit) component of β2-integrin



Developed at CIEMAT, in partnership with UCL

- CD34+ cells are mobilized to PB with G-CSF and plerixafor
- Cells are collected via apheresis
- Following transduction & cryopreservation, TDM-Busulfan conditioning is administered prior to infusion of RP-L201

RP-L201 Clinical Trial and Outcome Measures

Trial Design – Non-Randomized Global Phase 1/2 Study

Phase	N (Planned)	N (Treated)
1	2	2
2	7	2

→ Data from N=3 subjects described
N=1 subject recently treated

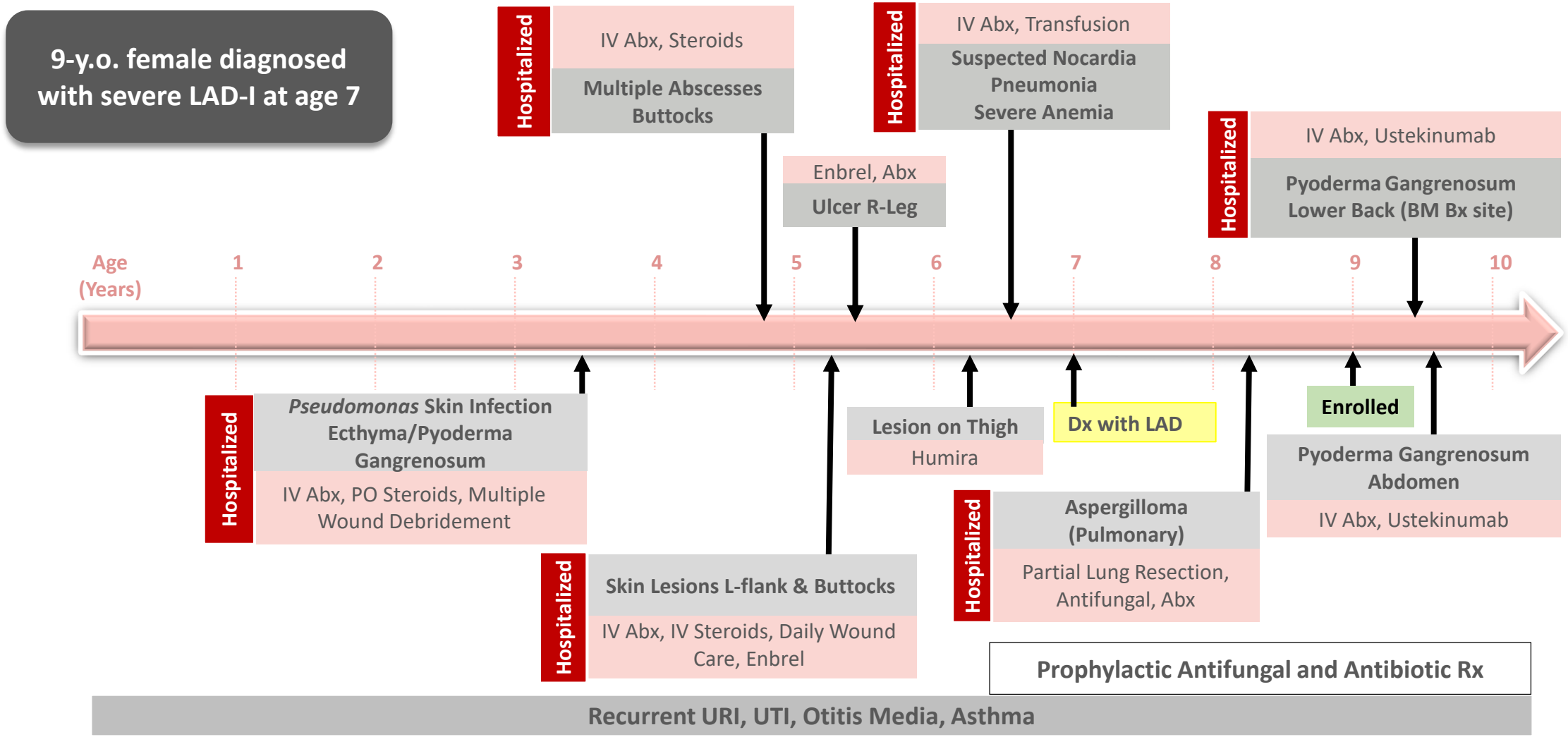
Primary Outcomes

- **Phase 1:**
  - Safety & preliminary efficacy
- **Phase 2:**
  - Survival: proportion of patients alive at age 2 and at least 1-year post infusion (& not requiring alloHSCT)
  - Safety

Secondary Outcomes

- % of pts w/neutrophil CD18 expression at least 10% of normal
- % of pts w/neutrophil VCN of at least 0.1 copies/cell at 6m post-rx
- Incidence and severity of infections
- Improvement/normalization of neutrophilia
- Resolution (partial or complete) of underlying skin rash or periodontal abnormalities

Medical History of Subject L201-003-1001



Historical patient records collected by UCLA Mattel Children's Hospital
LAD has received CIRM Funding

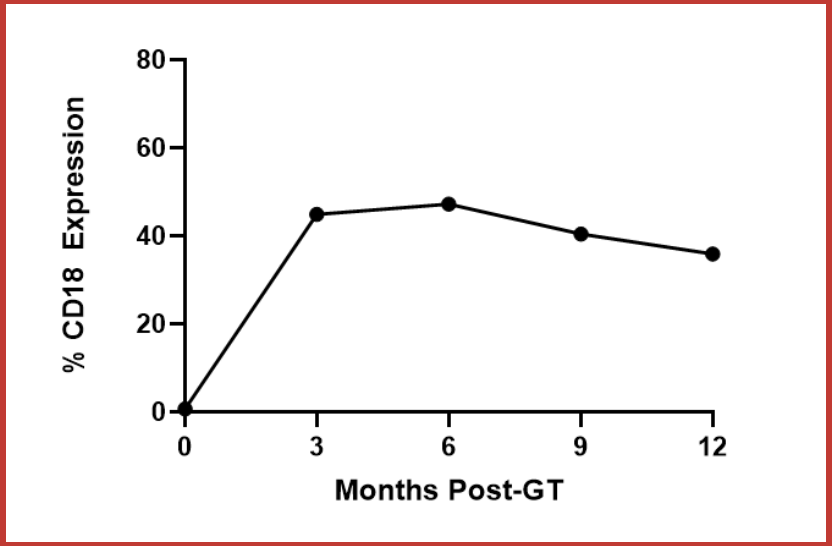
Subject L201-003-1001: 12 Month Follow-Up

Key Drug Product Metrics

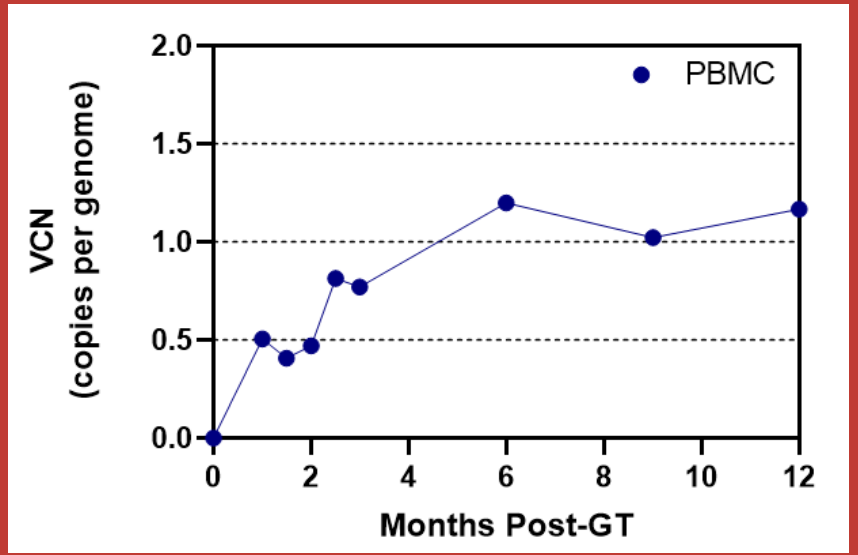
CD34+ Cell Dose: 4.2 x 10^6 cells/kg

Drug Product VCN: 3.8

% CD18 Expression (PMN)



VCN (PBMC)

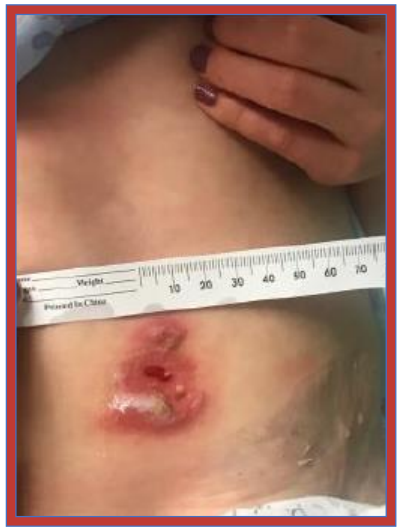


PMN: polymorphonuclear lymphocytes

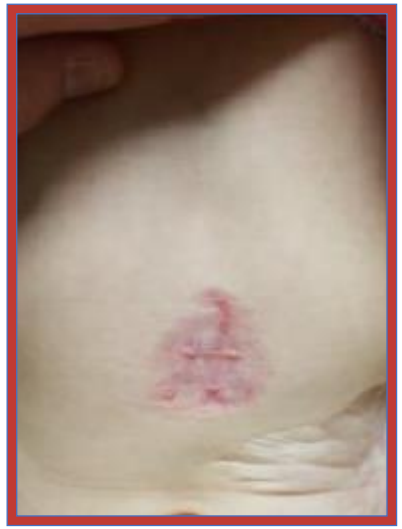
PBMC: peripheral blood mononuclear cell

RP-L201: Visible Improvements Post-Treatment

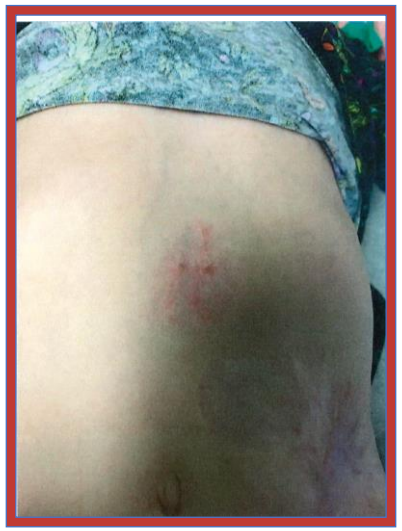
Spontaneous Abdominal Lesion



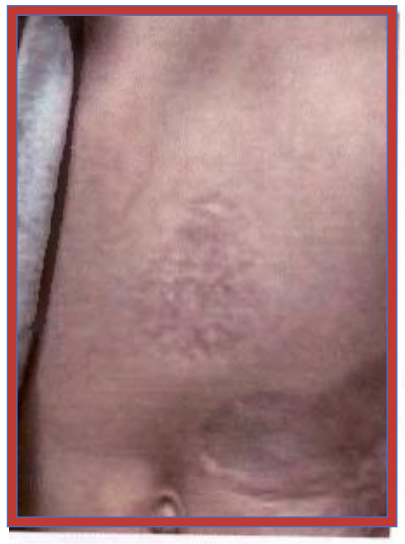
Baseline (Pre-Treatment)



3M



6M



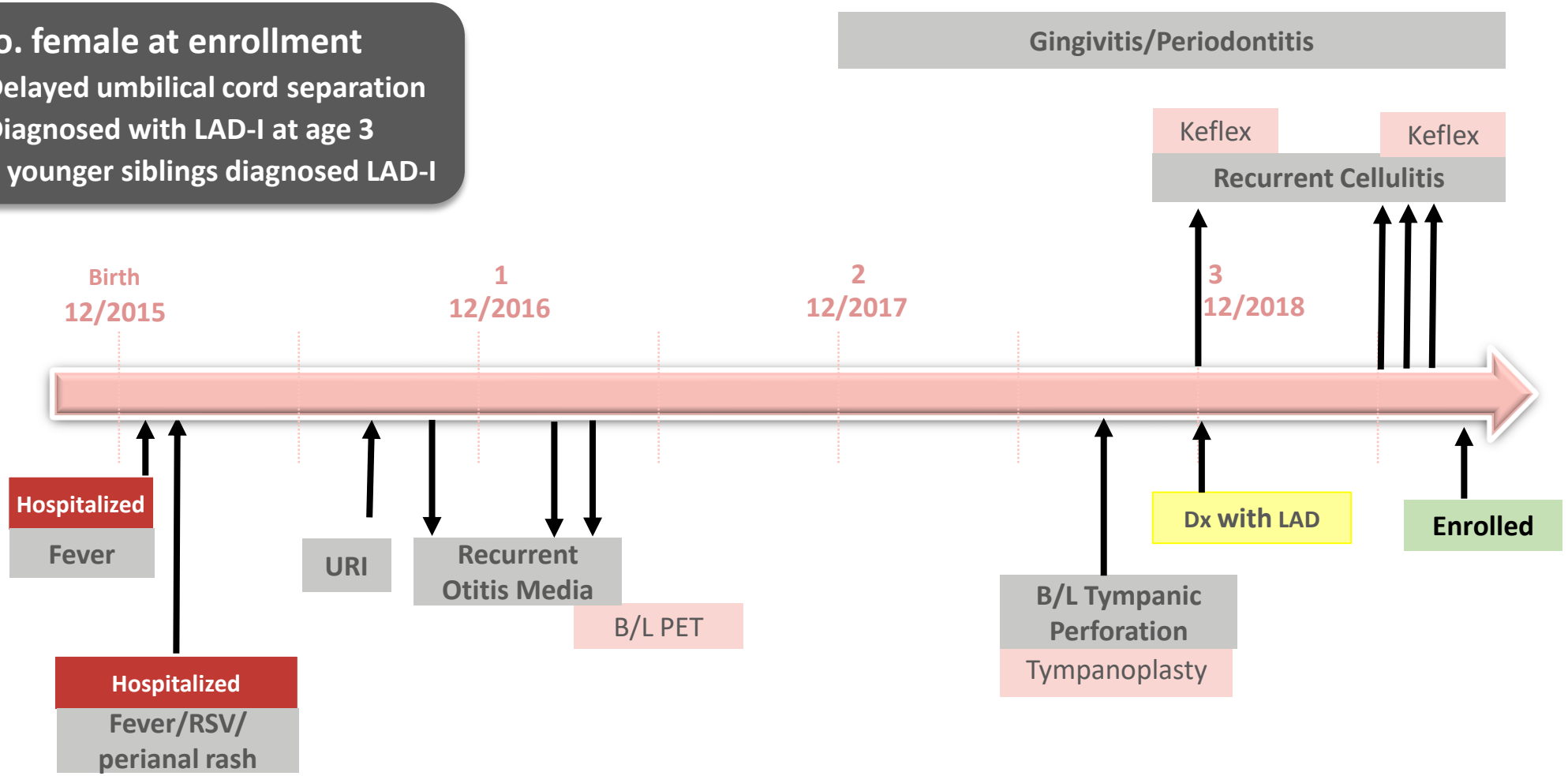
12 M

UCLA Mattel Children's Hospital Data
LAD has received CIRM Funding

Medical History of Subject L201-003-1004

3-y.o. female at enrollment

- Delayed umbilical cord separation
- Diagnosed with LAD-I at age 3
- 2 younger siblings diagnosed LAD-I



Historical patient records collected by UCLA Mattel Children's Hospital
LAD has received CIRM Funding

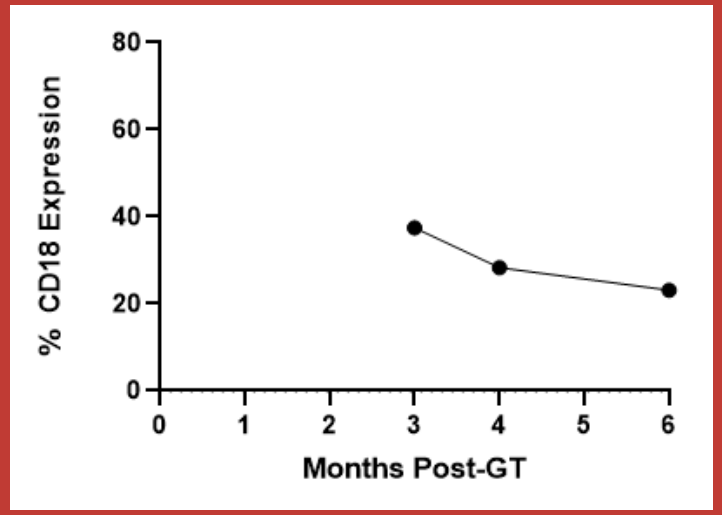
Subject L201-003-1004: 6 Month Follow-Up

Key Drug Product Metrics

CD34+ Cell Dose: **2.8 x 10^6 cells/kg**

Drug Product VCN: **2.5**

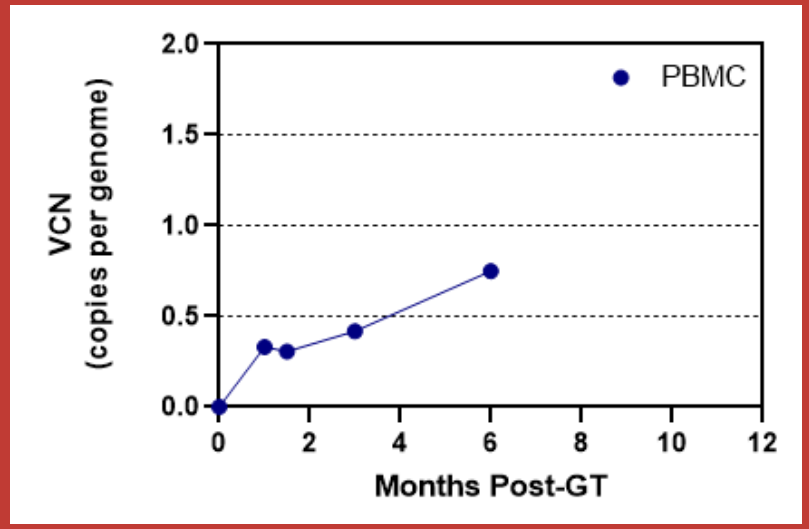
% CD18 Expression (PMN)



CD18 at baseline was reported as dim in approximately 63% PMNs, likely indicating an unstable protein, and in the context of additional clinical and laboratory evidence of severe LAD-I

PMN: polymorphonuclear lymphocytes

PBMC VCN

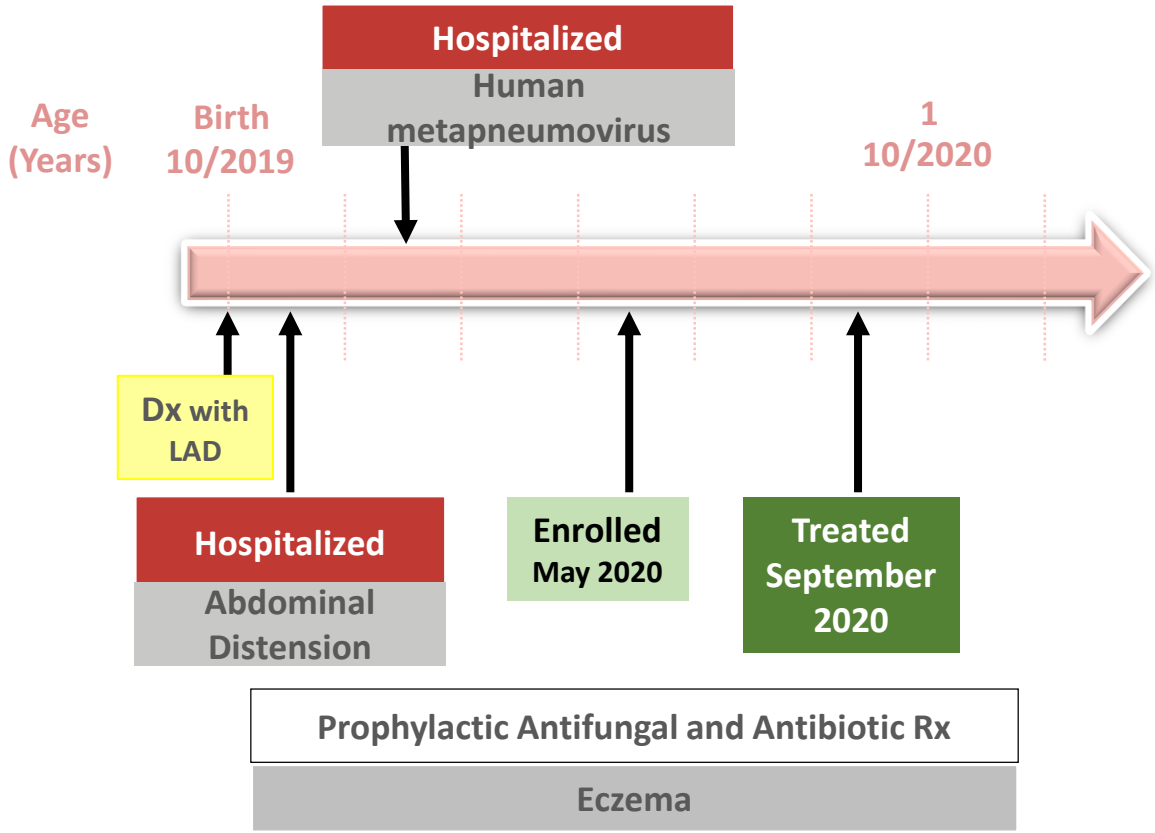


PBMC: peripheral blood mononuclear cell

Medical History of Subject L201-003-2006

7 m.o. male at enrollment

- Diagnosed at birth given family history of disease
- Delayed separation of umbilical cord (6 weeks)
- 2 older siblings diagnosed with severe LAD-I



Key Drug Product Metrics

CD34+ Cell Dose: 4.3×10^6 cells/kg

Drug Product VCN: 2.87

Hematopoietic reconstitution observed Day 35 post-infusion

Clinically stable with no reported serious adverse events post-infusion

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LAD has received CIRM Funding

Conclusions

- **Three severe LAD-I patients have been successfully infused with RP-L201, an *ex-vivo* LV autologous HSPC gene therapy**

- **Safety profile of RP-L201 appears favorable**
  - Infusion well tolerated; no drug product-related SAEs or severe AEs

- **Preliminary efficacy evident in both subjects with ≥ 6-months of follow-up**
  - Subject L201-003-1001 with durable CD18 PMN expression ~40% and PB VCN of 1.2 at 12-months post-infusion and resolution of existing skin lesions
  - Subject L201-003-1004 with CD18 PMN expression 23% 6-months post-treatment and PB VCN kinetics during initial 3 months similar to those of first subject

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