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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62nd American Society of Hematology (ASH) Annual Meeting and Exposition
December 7, 2020

Abstract #142484
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: 2-30% CD18+ PMN
Severe: <2% 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

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

- 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**

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<th>Phase</th>
<th>N (Planned)</th>
<th>N (Treated)</th>
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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
9-y.o. female diagnosed with severe LAD-I at age 7

- **IV Abx, Steroids**
  - Multiple Abscesses Buttocks

- **Hospitalized**

- **IV Abx, Transfusion**
  - Suspected Nocardia Pneumonia
  - Severe Anemia

- **Hospitalized**

- **Enbrel, Abx**
  - Ulcer R-Leg

- **Hospitalized**

- **IV Abx, Ustekinumab**
  - Pyoderma Gangrenosum
  - Lower Back (BM Bx site)

- **Hospitalized**

- **IV Abx, PO Steroids, Multiple Wound Debridement**

- **Hospitalized**

- **Pseudomonas Skin Infection**
  - Ecthyma/Pyoderma Gangrenosum
  - IV Abx, PO Steroids, Multiple Wound Debridement

- **Hospitalized**

- **Lesion on Thigh**
  - Humira

- **Enrolled**

- **Aspergilloma (Pulmonary)**
  - Partial Lung Resection, Antifungal, Abx

- **Hospitalized**

- **Skin Lesions L-flank & Buttocks**
  - IV Abx, IV Steroids, Daily Wound Care, Enbrel

- **Hospitalized**

- **Lesion on Thigh**
  - Humira

- **Hospitalized**

- **Pyoderma Gangrenosum Abdomen**
  - IV Abx, Ustekinumab

- **Hospitalized**

- **Prophylactic Antifungal and Antibiotic Rx**

- **Recurrent URI, UTI, Otitis Media, Asthma**

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: $4.2 \times 10^6$ cells/kg
- Drug Product VCN: 3.8

% CD18 Expression (PMN)

- PMN: polymorphonuclear lymphocytes

VCN (PBMC)

- PBMC: peripheral blood mononuclear cell
RP-L201: Visible Improvements Post-Treatment

Spontaneous Abdominal Lesion

Baseline (Pre-Treatment)  3M  6M  12 M
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: \(2.8 \times 10^6\) 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

PMBC: 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

Birth
10/2019

Abdominal Distension
10/2019

Hospitalized
Human metapneumovirus
10/2020

Enrolled
May 2020

Dx with LAD

Treated
September 2020

Prophylactic Antifungal and Antibiotic Rx

Eczema

Key Drug Product Metrics
CD34+ Cell Dose: $4.3 \times 10^6 \text{ cells/kg}$
Drug Product VCN: 2.87

Hematopoietic reconstitution observed Day 35 post-infusion

Clinically stable with no reported serious adverse events post-infusion

Historical patient records collected by UCLA Mattel Children’s Hospital
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
Acknowledgements

Dayna Terrazas RN
Augustine Fernandes PhD
Caroline Kuo MD
Satiro De Oliveira MD
Theodore Moore, MD

Rocket Pharmaceuticals, Inc.
Elena Almarza, PhD
Gayatri R. Rao, MD, JD
Ken Law, PhD
Brian Beard, PhD
Jonathan Schwartz, MD²

Cristina Mesa-Núñez, PhD
Juan Bueren, PhD

Claire Booth MBBS PhD MSc
Adrian Thrasher MB PhD FMedSci

Julián Sevilla, MD, PhD