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

Abstract # 1574

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Introduction

- *ITGB2* gene mutations affect the common chain (CD18) of the beta2-integrin family and prevent functional CD18/CD11 heterodimer expression on leukocyte cell surfaces – essential for cell adhesion and subsequent tissue migration.
- Severe leukocyte adhesion deficiency-I LAD-I is characterized by recurrent and ultimately fatal disseminated infections.
- Current Treatment Option: Allogeneic hematopoietic stem cell transplantation (HSCT) – limited by donor availability, infections, frequent GvHD and graft failure.
- Patients suffer from recurrent infections; fatal in majority[1]
  - 60–75% patients with severe LAD-I: death **prior to age 2**
  - >50% patients with moderate LAD-I: death **prior age 40**

LAD-I Disease Spectrum

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

Kaplan-Meier Survival Estimates by Neutrophil CD18 Expression

In patients with severe and moderate LAD-I (by CD18 expression) not receiving allogeneic HSCT

39% survival to age 2 years for 66 evaluable patients with severe LAD-I (CD18 expression <2%) not receiving allogeneic HSCT

- <2% CD18 Expression
- 2%–4% CD18 Expression
- >4%–10% CD18 Expression
- >10% CD18 Expression

HSCT: hematopoietic stem cell transplantation; PMN: polymorphonuclear leukocytes. [1] [1] Almarza E et al. *J Allergy Clin Immunol Pract*. 2018 July-August (6) 1418-1420.

End Points

Primary Outcomes

Phase 1:

- Safety and preliminary efficacy

Phase 2:

- Survival: Proportion of patients alive at least 1-year post-infusion and at age 2 in the absence of allogeneic HSCT
- Safety

Secondary Outcomes

- Reduction in the incidence of significant infections (i.e., requiring I.V. antimicrobials/hospitalization) and prolonged (≥7 days) infection-related hospitalizations
- % of patients with neutrophil CD18 expression at least 10% of normal
- % of patients with neutrophil VCN of ≥0.1 at 6 months post-RP-L201 infusion
- Improvement / normalization of leukocytosis and neutrophilia
- Resolution (partial or complete) of underlying skin rash or periodontal abnormalities

Key Eligibility

- 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

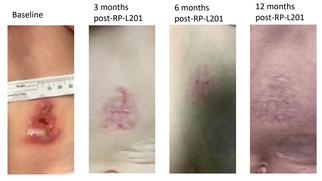
Interim Results

Patient Demographics and Investigational Product Metrics

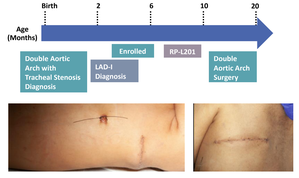
Patient	Sex	Age at enrollment	Investigational Product VCN	CD34+ Cell Dose
L201-003-1001	F	9 years	3.8	4.2×10^6 cells/kg
L201-003-1004	F	3 years	2.5	2.8×10^6 cells/kg
L201-003-2005	F	3 years	1.8	6.5×10^6 cells/kg
L201-003-2006	M	7 months	2.9	4.3×10^6 cells/kg
L201-003-2007	M	3 months	3.6	5.0×10^6 cells/kg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

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

L201-003-1001: Spontaneous resolution of abdominal lesion

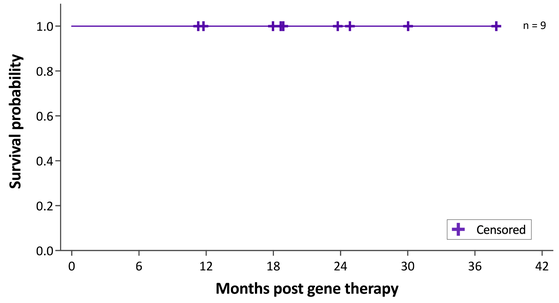


L201-004-2008: Wound repair at thoracotomy site after surgical correction of double aortic arch



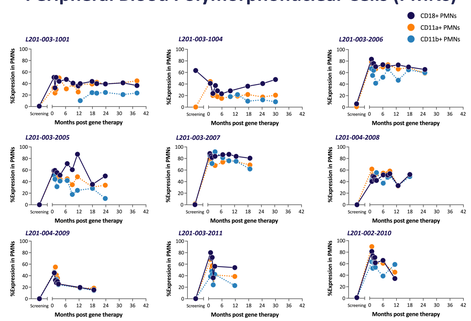
As of November 2, 2022: Data reported from 9 of 9 patients (12–36m follow-up). Study enrollment is completed. All subjects have been treated. Preliminary interim results are presented from the ongoing clinical study.

100% Overall Survival at 1-year Post RP-L201 and to 2 Years of Age



All nine patients met the primary endpoint:
Survival at 1-year post-RP-L201 infusion (and to >2 years of age for those age <1y) without allogeneic HSCT

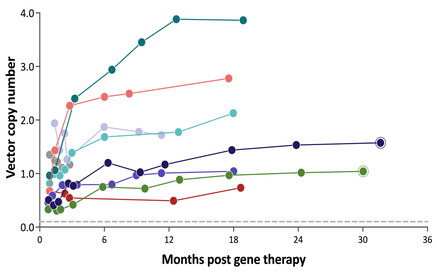
CD18/CD11 Expression in Peripheral Blood Polymorphonuclear Cells (PMNs)



Durable CD18 restoration in PMNs which correlates with CD11a & CD11b co-expression

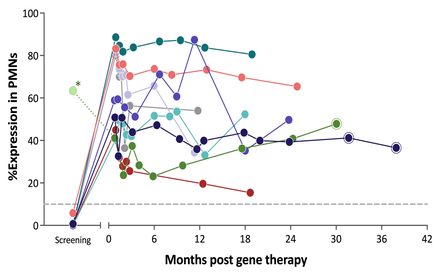
CD11a and CD11b were determined in clone 6.7 CD18+ PMNs. Data Cut: November 2, 2022

Vector Copy Number in Peripheral Blood Mononuclear Cells



Durable provirus integration >12 months following gene-corrected cell infusion across the entire cohort

CD18 Expression in Peripheral Blood Polymorphonuclear 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
- Assessed on LTFU Trial
- VCN 0.1

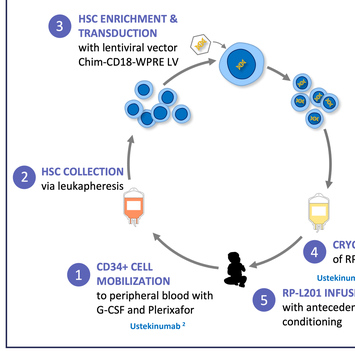
* Dim/weak CD18 expression reported at baseline for Subject L201-003-1004 in ~63% of cells in conjunction with <2% CD11a/CD11b expression, likely indicating abnormal/unstable protein

Sustained >10% PMN CD18 expression after 1 year of gene-corrected cell infusion across the entire cohort

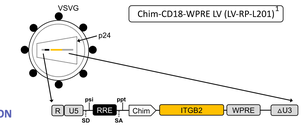
RP-L201 Study Design

Trial Design

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



***Ex-vivo* lentiviral vector gene therapy consisting 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.**



[1] Developed at CIEMAT, in partnership with UCL
[2] Ustekinumab 2 weeks prior mobilization and 1–2 weeks prior RP-L201 infusion
[3] Therapeutic drug monitoring during myeloablative busulfan conditioning with target busulfan exposure of 75.0m mg/L*h (cumulative AUC).

Conclusions

- **All (9 out of 9)** severe LAD-I patients have successfully received RP-L201; currently with 12–36 months of follow-up
- Infusion has been **well tolerated**; no investigational product- (RP-L201) related serious adverse events (SAEs)
- Safety profile of RP-L201 appears favorable
- Initial integration site analysis (**ISA**) indicates **highly polyclonal patterns** without evidence of dominant integrations in proximity to oncogenic *loci*
- Efficacy evident in **9 out of 9 patients**, including **all patients with ≥12 months of follow-up**
  - **Sustained >10% CD18 polymorphonuclear cell (PMN) expression** (Range: 15.4%–88.6%, Median: 56.3%) with concomitant durable >0.1 VCN integration across the cohort
  - **100% overall survival** (OS), including 100% OS one-year post-RP-L201 and to 2 years of age
  - **No typical LAD-I infections** since gene-corrected cell engraftment
  - Evidence of spontaneous **resolution** of LAD-I-related **skin rash** and **restoration of wound repair** capabilities

Disclosures: Booth: SOBI: Consultancy, Honoraria; Orchard Therapeutics: Consultancy, Honoraria; Takeda: Honoraria; Rocket Pharmaceuticals, Inc.: Consultancy; GSK: Honoraria. Sevilla: Inventor on patents on lentiviral vectors filed by CIEMAT, CIBERER and Fundación Jiménez Díaz, and may be entitled to receive financial benefits from the licensing of such patents. Rocket Pharmaceuticals, Inc.: Consultant, Patents & Royalties, Licensed Medical Products. Consultant/ Advisor/Honorarium for the following: Amgen, Novartis, Miltenyi, Sobi. Rao: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. Lopez: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. Almarza: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. Terrazas: There are no relationships to disclose. Zubicaray: Novartis: Consultancy. González-Vicent: There are no relationships to disclose. Chetty: There are no relationships to disclose. G O'Toole: There are no relationships to disclose. J Xu-Bayford: There are no relationships to disclose. E Nicoletti: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. A Fernandes: There are no relationships to disclose. C Kuo: There are no relationships to disclose. De Oliveira: Bluebird Bio: Research Funding; Orchard Therapeutics: Research Funding. Moore: MD Choi: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. M Zeini: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. C Mesa-Núñez: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. Thrasher: Orchard Therapeutics: Consultancy and Equity Ownership; Rocket Pharmaceuticals, Inc.: Consultancy; 4Bio Capital: Consultancy; Generation Bio: Consultancy and Equity Ownership. Schwartz: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. Kohn: Consultancy and Scientific Advisory Board Member: Allogene Therapeutics, Pluto Therapeutics, ImmunoVec, MyoGeneBio.