Administration of KRESLADI™ (marnetegragene autotemcel), also known as RP-L201*

ICD-10 Coordination and Maintenance Committee Meeting
March 19-20, 2024

* RP-L201 will also be referred by the trade name KRESLADI™ (marnetegragene autotemcel) upon FDA approval

RP-L201 is an investigational therapy that has not been approved by any regulatory authority. The safety and effectiveness of RP-L201 has not yet been established.

RP-L201 is a gene therapy in late-stage development for the treatment of severe LAD-I

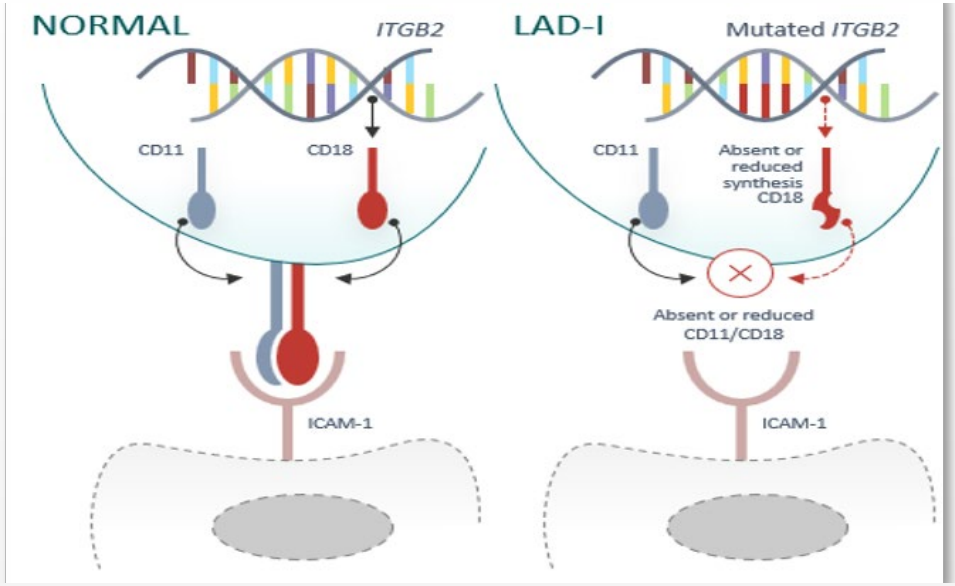
RP-L201 for treatment of Severe LAD-I
Leukocyte Adhesion Deficiency-I

LAD-I Etiology	• Rare, inherited primary immunodeficiency disorder • Caused by defects in the *ITGB2* gene • Causes a deficiency in leukocyte CD18 expression
Disease Characteristics	• Recurrent severe infections resulting in frequent hospitalizations[1] • 61%-75% of patients with severe LAD-I die before 2 years of age in the absence of alloSCT[2,3] • ~1 case per 1 million individuals globally with 60% categorized as severe[4]
Standard of Care	• AlloSCT is the current standard of care for treating severe LAD-I • Availability of matched donors for alloSCT is a barrier to treatment • AlloSCT associated with high rates of transplant-related mortality and morbidity
RP-L201 Product Information	One-time gene therapy consisting of autologous HSCs genetically modified with a lentivirus containing a functional copy of the *ITGB2* gene to facilitate the expression of functional CD18 and restore immune function
Code Request	• Currently no ICD-10-PCS code exists to specifically describe the administration of RP-L201 • Unique coding will allow for appropriate tracking, reporting, and outcomes research of RP-L201

Source: 1. Rocket Data on File (Natural History Study Report); 2. Almarza E et al. J Allergy Clin Immunol Pract. 2018;6(4):1418-1420; 3. Fisher A et al. Immunodeficiency Reviews. 1988;1:39-54; 4. Cox and Weathers Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;105(1);86-90

Severe LAD-I is a rare primary immunodeficiency characterized by recurrent severe infections resulting in frequent hospitalizations, with nearly universal childhood mortality

A heterodimeric complex of CD18 and CD11 is expressed on the surface of leukocytes[1]



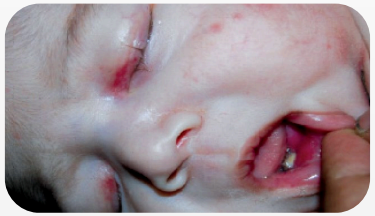
Deficiencies in CD18 prevent normal CD11 / 18 heterodimer cell surface expression, impairing neutrophil extravasation to infected and inflamed tissues[2], which is crucial for neutrophil mediated responses to viral, bacterial, and fungal infections

- Severe LAD-I is associated with a high degree of childhood mortality in the absence of alloSCT
- Mortality at 2 years of age in the absence of alloSCT is 61%-75%[3,4]
- Due to donor availability limitations, patient-related factors, and other considerations, a substantial proportion of children are unable to receive alloSCT[5]

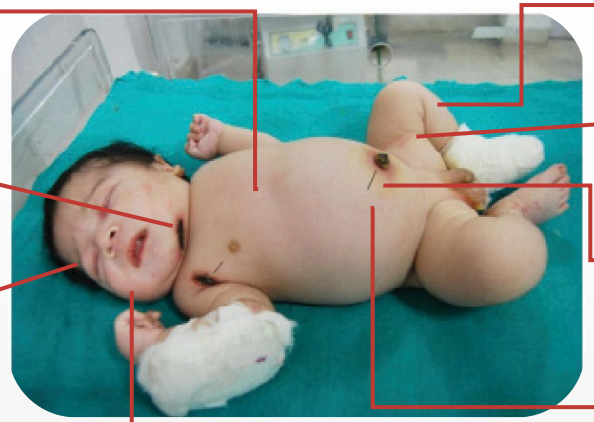
Sources: 1. Gu et al. Comp Med 2004;54(4):363-72; 2. Tan. Biosci Rep. 2012; 32(3): 241-69; 3. Almarza E et al. J Allergy Clin Immunol Pract. 2018;6(4):1418-1420; 4. Fisher A et al. Immunodeficiency Reviews. 1988;1:39-54; 5. Gragert et al. N Engl J Med. 2014; 371(4): 339-348; Abbreviations: LAD-I: Leukocyte Adhesion Deficiency I; AlloSCT: Allogeneic Stem Cell Transplant

Patients with severe LAD-I experience recurrent skin rashes, inadequate wound repair, periodontitis, and multiple systemic complications leading to physical pain and emotional distress

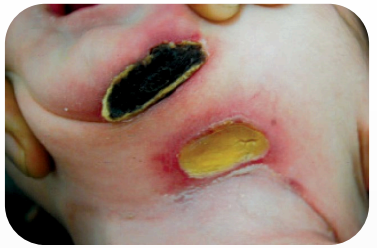
Severe LAD-I Signs & Symptoms[1,2,3]



- ***Recurrent severe skin infections, non-responsive to antimicrobials***
- *Inadequate wound repair*
- *Leukocytosis*
- *Gingivitis & periodontitis, often resulting in severe bone and tooth loss*[4,5]



- *Infection without pus formation*
- *Skin rashes*
- *Infected umbilical cord*
- *Delayed umbilical detachment*

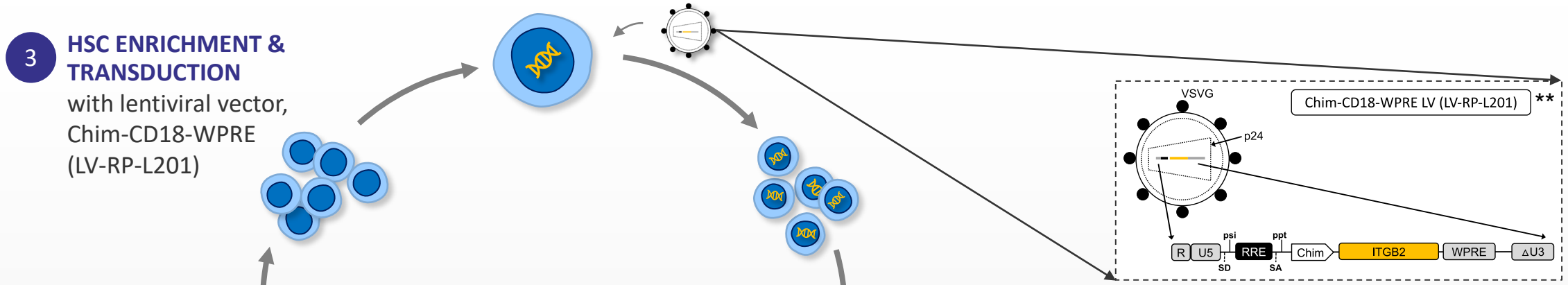


Throughout their childhood, patients experience **accumulative disease burden and reduced quality of life** from repeated infectious episodes[6], making **timely diagnosis and treatment imperative**

Sources: 1. Almarza et al. J Allergy Clin Immunol Pract. 2018;6(4):1418-1420; 2. Bakhtiar et al. Blood Adv. 2021;5(1);262-273; 3. Ahmad et al. Iran Path. 2013;8(3);204-208 4. Moutsopoulos et al. Sci Transl Med. 2014;6(229);229ra40; 5. Jiang et al. Allergy Asthma Clin Immunol 2015;1(27); 5. Hajishengallis and Moutsopoulos Microb Pathog. 2016 May;94:21-6 6. Tabolli et al. Front Immunol. 2014;5(605); Abbreviations: LAD-I: Leukocyte Adhesion Deficiency-I; HRQoL: Health-Related Quality of Life

RP-L201 is a disease-correcting LV gene therapy option for patients with severe LAD-I that provides a normal copy of the *ITGB2* gene[1], facilitating the production of functional CD18

RP-L201 Gene Therapy Process Overview



3 HSC ENRICHMENT & TRANSDUCTION
with lentiviral vector, Chim-CD18-WPRE (LV-RP-L201)

4 CRYOPRESERVATION
of RP-L201

Ustekinumab*

5 RP-L201 INFUSION
with 4 days of antecedent **Busulfan*****
conditioning and infusion 24-48 hours afterwards

1 CD34⁺ CELL MOBILIZATION
to peripheral blood with G-CSF and Plerixafor
Ustekinumab*

2 HSC COLLECTION
via leukapheresis

Preclinical and clinical studies suggest that gene therapy with **lentiviral vectors in hematopoietic stem cells** has the potential to support **phenotype correction** in primary immunodeficiency diseases such as LAD-I[2]

*Ustekinumab administered 2 weeks prior to mobilization and 1–2 weeks prior RP-L201 infusion; **Developed at CIEMAT, in partnership with UCL; ***Therapeutic drug monitoring during myeloablative busulfan conditioning with target busulfan exposure of 75.0 mg/L*h (cumulative AUC). Sources: 1. Booth et al. Blood 2022;140(Supplement 1);7774-7775 2. Fischer et al. Clin Genet 2015;88(6):507-15; See slide notes for abbreviations

RP-L201 was studied in a single-arm Phase I / II trial in patients diagnosed with severe LAD-I to explore key efficacy and safety outcomes

Trial Design[1]

Non-Randomized, Single-Arm, Global Phase 1 / 2 Study (N=9)

Primary Endpoints[1]

Phase 1

- Preliminary efficacy
- Safety

Phase 2

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

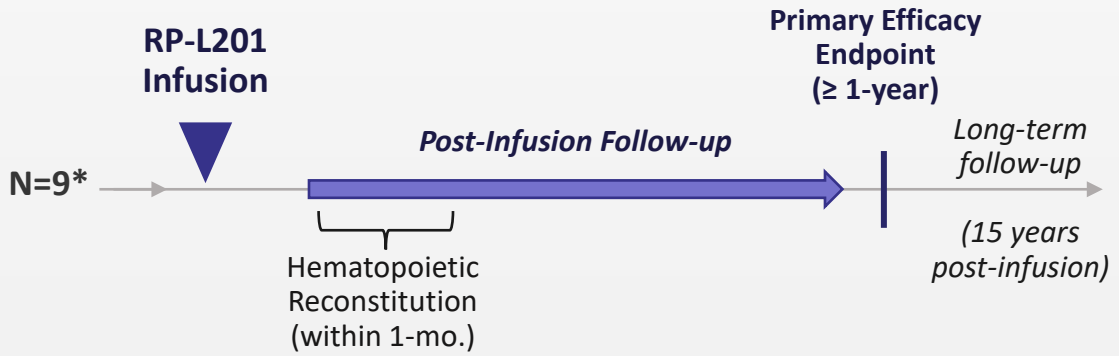
Eligibility Criteria[1]

- 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

Secondary Endpoints[2]

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

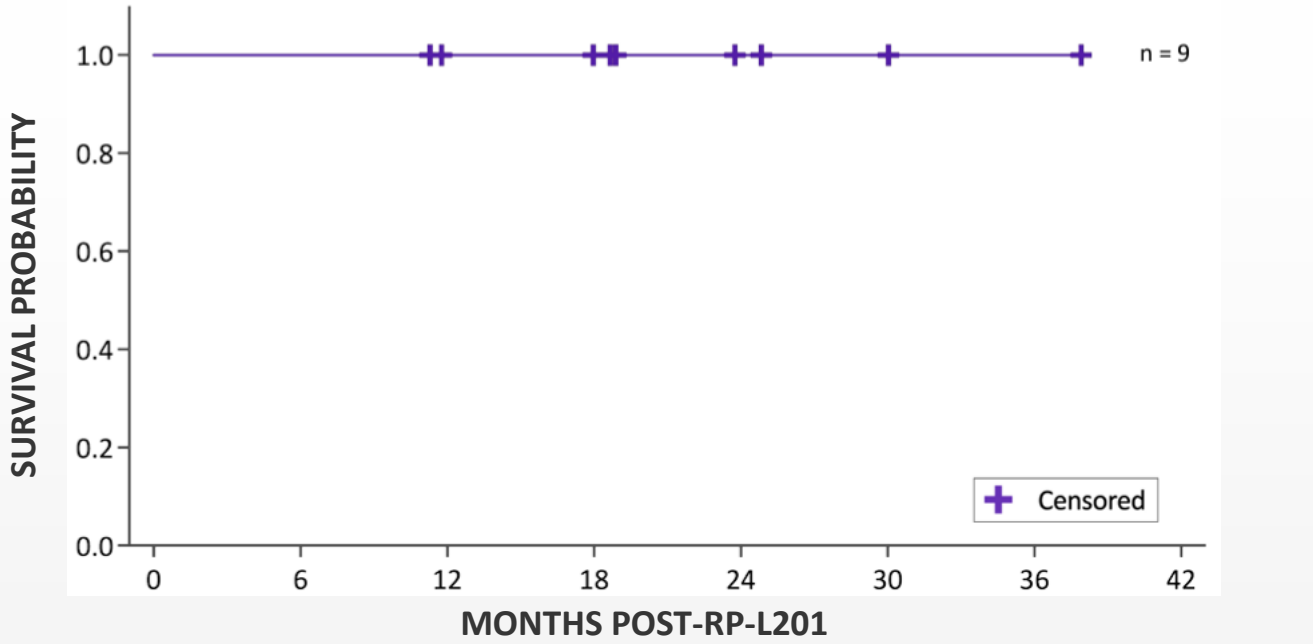
Trial Timeline[3]



*N=2 patients were enrolled in a Phase I trial first, then N=7 additional patients were added as part of the Phase II continuation; **Or alive at the age of 24 months without alloSCT if patients were less than 1 year of age at study enrollment; Source: 1. A Clinical Trial to Evaluate the Safety and Efficacy of RP-L201 in Subjects With Leukocyte Adhesion Deficiency-I. ClinicalTrials.Gov; 2. Rocket data on file (CTD 2.7.3); 3. RP-L201-0318 Protocol Version 2.3; See slide notes for abbreviations

RP-L201 met its endpoint, demonstrating survival for all patients at 12 months, and continued to collect data up to 36 months, with patients maintaining alloSCT-free survival

AlloSCT-Free Survival Kaplan-Meier Estimate[1]



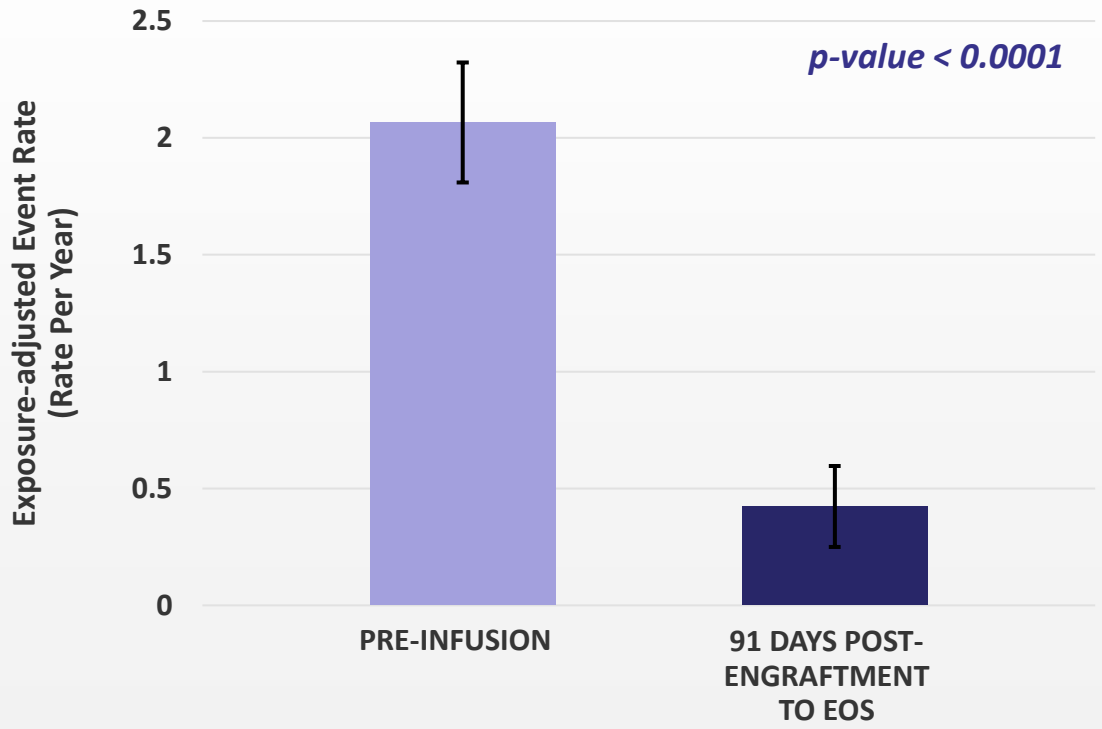
PRIMARY ENDPOINT: The trial met the primary endpoint of survival at least 1-year post-RP-L201 without alloSCT and at age 24 months without alloSCT for patients less than 1 year of age at enrollment

SECONDARY ENDPOINT: The trial met the secondary endpoints of alloSCT-free survival of 100% without any incidences of GF or aGvHD

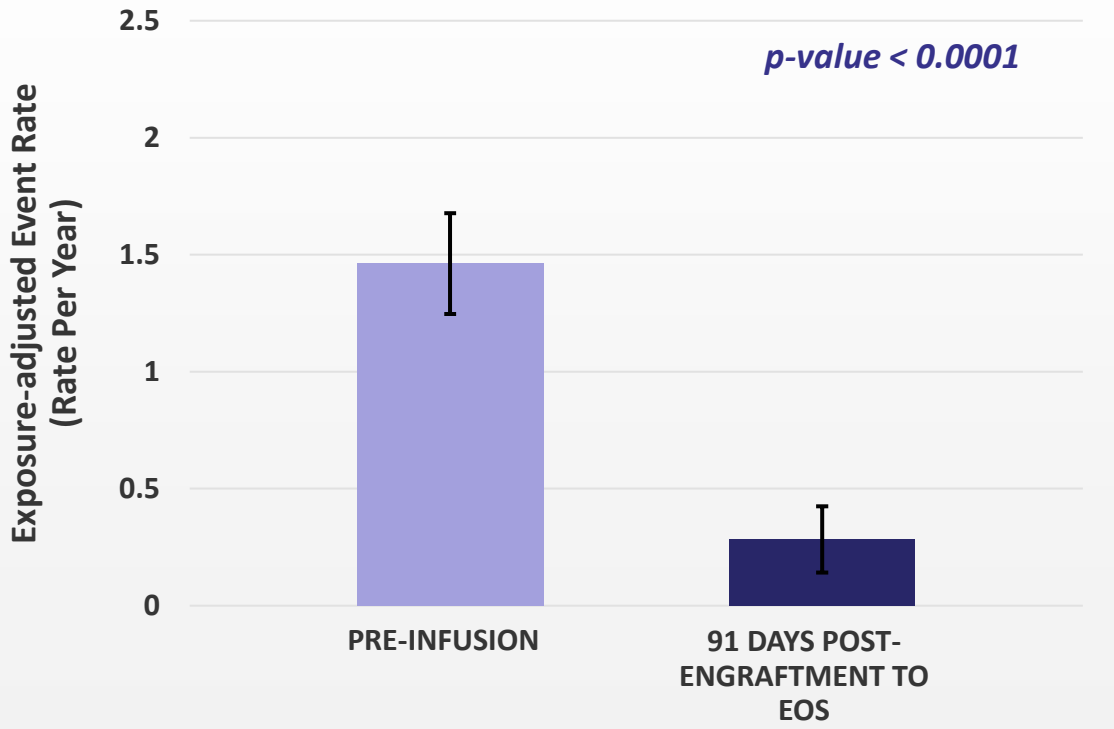
Source: 1. Kohn DB et al., ASGCT #1574, 2023 - Data cutoff on January 24, 2023; Abbreviations: aGvHD: Acute Graft Versus Host Disease; AlloSCT: Allogeneic Stem Cell Transplant; GF: Graft Failure; LAD-I: Leukocyte Adhesion Deficiency-I; PMN: Polymorphonuclear Cell; VCN: Vector Copy Number

Through the 24-month post-infusion follow-up duration, RP-L201 treatment significantly reduced the incidence of prolonged and overall infection-related hospitalizations

*Incidence of Infection-Related Hospitalizations[1]**



*Incidence of Prolonged (≥ 7 days) Infection-Related Hospitalizations[1]**



*Reported as of 3–24-month follow-up; Sources: 1. Rocket Data on File (RP-L201-0318 SR v1.0) - Data cutoff on January 24, 2023; Abbreviations: EOS: End of Study

RP-L201 was generally well-tolerated; the treatment was associated with no treatment-related adverse events or serious infusion-related adverse events up to 36 months of follow-up[1,2]

No RP-L201-related adverse events have been reported[3]

- Data are available from **9 / 9 patients with 12–36 months follow-up** after receiving RP-L201
- The **safety profile** of RP-L201 **appears favorable**
  - Initial insertion site analysis (ISA) indicates **highly polyclonal patterns** without evidence of dominant integrations in proximity to oncogenic *loci*
  - Replication-competent lentivirus (RCL) testing have indicated **uniformly negative results** in all subjects after RP-L201 infusion to-date

Adverse Events Related to Other Study Procedures[3]*

Conditioning-Related SAE	Conditioning and LAD-I Related SAE
Veno-occlusive disease (VOD)	Pulmonary arterial hypertension (PAH)
Grade 3	Grade 4
Resolved without subsequent complications	PAH **resolved**; deemed secondary to busulfan in the context of severe pre-treatment pneumonias and concomitant double aortic arch with tracheal compression **which was surgically corrected *after* RP-L201 with normal wound healing**

*Including busulfan conditioning; Sources: 1. Kohn DB et al., ASGCT #1574, 2023; 2. Rocket Pharmaceuticals Website, 2022 (Accessed 20 October 2023); 3. Rocket Data on File (RP-L201-0318 CSR v1.0)- Data cutoff on January 24, 2023; Abbreviations: AE: Adverse Event; Mo.: Month; SAE: Serious Adverse Event

Procedure Description, Documentation, and Current Coding

Procedure Description

Patients receive anti-inflammatory therapy approximately 2 weeks prior to initiation of HSPC mobilization and 1–2 weeks prior to infusion of RP-L201. Mobilization of $CD34^+$ HSPCs from blood is followed by transduction with the LV encoding for functional human CD18 *ITGB2* gene, followed by cryopreservation of the transduced HSPCs. If the amount of $CD34^+$ cells available for infusion is at least 2×10^6 viable CD34+ cells/kg, patients receive myeloablative conditioning with IV busulfan over 4 days and receive an infusion of gene-corrected HSPCs 24–48 hours after the final busulfan dose. Patients are infused with RP-L201 in the inpatient setting and hospitalized until HSPC reconstitution is determined.

Documentation

The healthcare provider will likely document RP-L201 in the pharmacy orders and clinical notes of the patient's electronic medical record (EMR). Providers may document the drug, dosage, administration, and any relevant outcomes in the EMR. Fields in which information about RP-L201 infusion may vary depending on the platform and software version utilized by the hospital/health system.

Current Coding

There is currently no ICD-10-PCS code to specifically describe the administration of RP-L201. A unique code will allow for appropriate tracking, reporting, and outcomes research for RP-L201.