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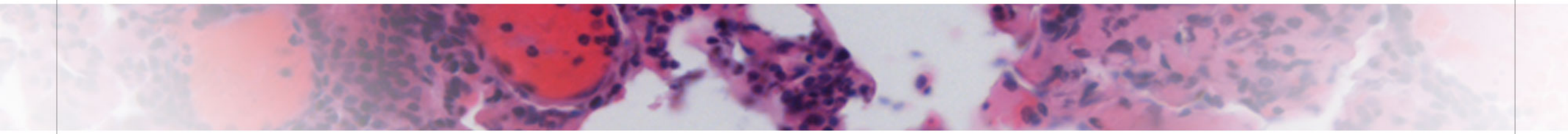


# Lentiviral Mediated Gene Therapy for Pyruvate Kinase Deficiency: Updated Results of a Global Phase 1 Study for Adult and Pediatric Patients

**Ami J. Shah, MD**

Center for Definitive and Curative Medicine
Department of Pediatrics, Division of Hematology, Oncology, Stem Cell Transplantation and Regenerative Medicine, Stanford University School of Medicine
Lucile Packard Children's Hospital Stanford

**José Luis López Lorenzo, MD; Susana Navarro, PhD; Julián Sevilla, MD, PhD; Lucía Llanos, MD, PhD; Begoña Pérez de Camino Gaisse, MD; Sol Sanchez, MD; Bertil Glader, MD, PhD; May Chien, MD; Oscar Quintana-Bustamante, PhD; Miriam Zeini, PhD; Grace Choi, BS; Eileen Nicoletti, MD; Gayatri R. Rao, MD, JD; Maria Grazia Roncarolo, MD; Juan A. Bueren, PhD; Jonathan D. Schwartz, MD; José C. Segovia, PhD**

**Abstract # 563**

# Disclosures

- Advisory Board: Orchard Therapeutics

# Introduction

- Pyruvate kinase deficiency (PKD) is a rare inherited hemolytic anemia caused by a mutation in the ***PKLR*** gene which results in decreased red cell pyruvate kinase activity and impaired erythrocyte energy production (glycolysis).
- Clinical manifestations include anemia, reticulocytosis, hyperbilirubinemia, splenomegaly, and iron overload and may be life threatening in severely affected individuals.

***PKD represents a significant unmet medical need***

- There are up to 8,000 cases in Europe and North America.
- Currently available therapies are palliative and limited to chronic blood transfusions, iron chelation therapy, and splenectomy.
- Side effects of these treatments include increased risk of disseminated infections and venous & arterial thromboembolic events.
- Therapies do not ameliorate PKD-related iron overload or end-organ damage.
- Allogeneic HSCT has been performed in select cases and resulted in transfusion independence; however, efficacy has been limited by significant toxicities and donor availability.

# Gene Therapy For PKD: Rationale

- Involves insertion of a functional *PKLR* gene into autologous hematopoietic stem and progenitor cells (HSPCs) with the intent of enabling red blood cell (RBC) pyruvate kinase enzyme production and normalized RBC function and lifespan
- Preclinical studies performed in Dr. Segovia's lab in a clinically relevant PKD murine model have demonstrated safety and efficacy.

**PKD mice transplanted with gene corrected cells demonstrated phenotypic correction:**

- Significantly increased RBC count and half-life
- Decreased reticulocytosis, erythropoietin levels, and iron overload
- Normalized spleen and liver size and structure

**Highly favorable safety profile:**

- No physical, behavioral, biochemical, hematologic, or morphologic abnormalities observed in transplanted mice
- Limited evidence of lentiviral vector in non-hematopoietic organs, indicating very low risk of germline transmission
- No evidence of replication competent lentivirus (RCL)

RP-L301-0119
NCT#04105166

# Global Phase 1 PKD Gene Therapy Study

## Clinical Sites:

Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain
Stanford University, Palo Alto, California, United States
Hospital Infantil Universitario Niño Jesús, Madrid, Spain

## Primary Endpoint

Evaluation of the safety and toxicity of RP-L301

## Secondary Endpoints

- Clinically significant reduction of anemia (Hb ↑)
- Transfusion independence at 12 months
- ≥ 50% reduction in transfusion requirements (when relevant) at 12 months
- Reduction of hemolysis
- Peripheral blood (PB) and bone marrow (BM) genetic correction as demonstrated by vector copy number (VCN)

## Key Eligibility Criteria

### Inclusion:

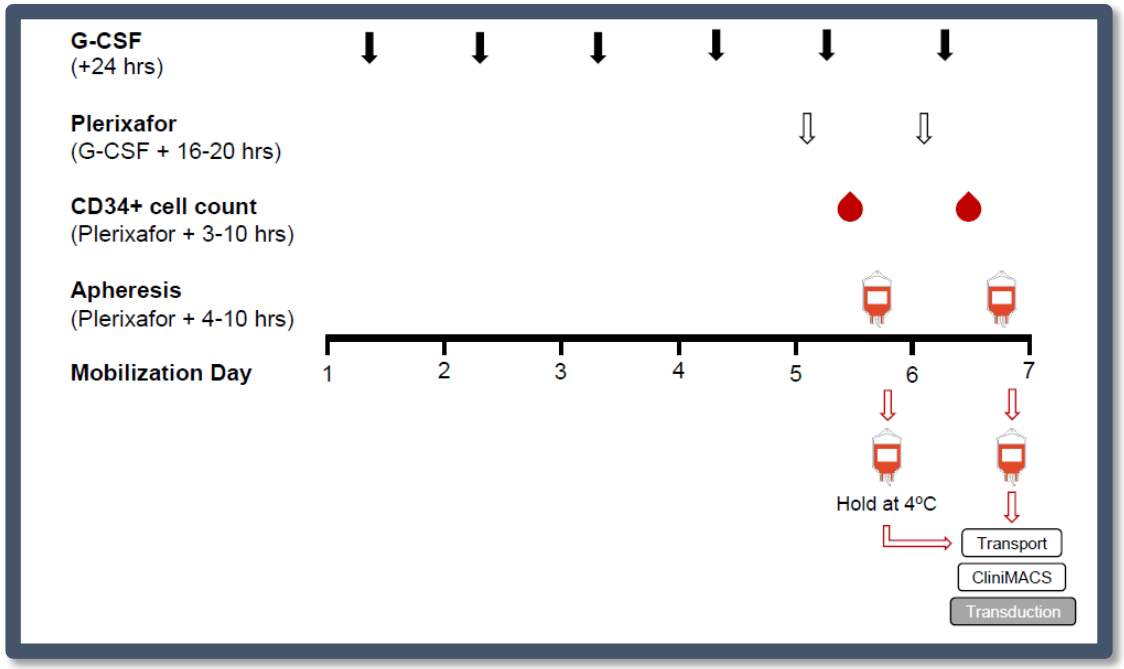
- PKD diagnosis with a confirmed *PKLR* mutation
- Age:
  - 1st cohort (N=2): ≥18 to 50 years
  - 2nd cohort (N=2): ≥12 to 17 years
  - 3rd cohort (N=2): ≥8 to 11 years
- Severe and/or transfusion-dependent anemia
- Adequate cardiac, pulmonary, renal, and hepatic function

### Exclusion:

- Presence of another known cause of hemolysis
- Venous or arterial thromboembolic event in prior 12 months
- Severe iron overload
- Other significant medical condition

# Study Design

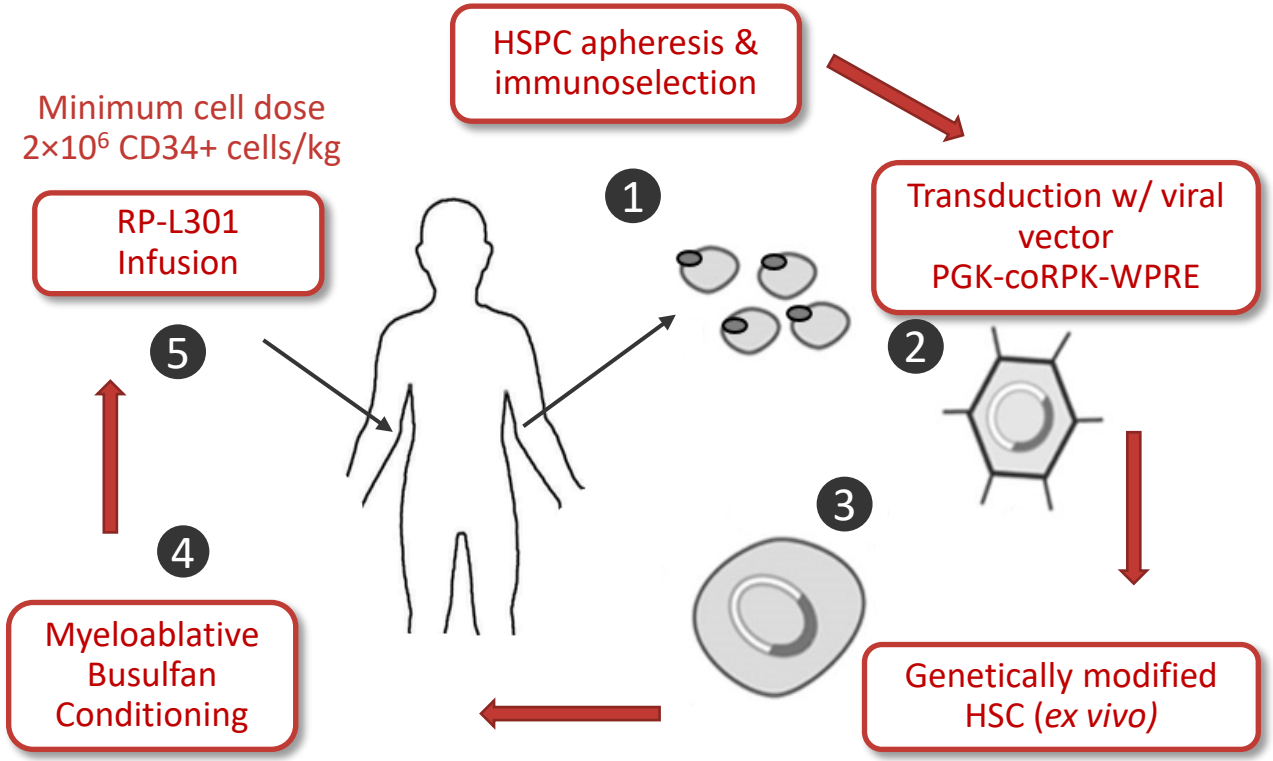
## CD34+ cell mobilization protocol with G-CSF and plerixafor:




G-CSF and plerixafor are administered over a 6-day sequence with apheresis conducted on 2 consecutive days.

PB counts of at least 10 CD34+ cells/µL are required to initiate apheresis.

## Schematic diagram of product manufacture and treatment:




Patients undergo HSPC mobilization and collection, followed by CD34+ immunoselection and transduction. RP-L301 is infused subsequent to myeloablative busulfan conditioning.

**(Target area under the curve: 73,125 ng/mL*hour over 4 days; TDM)**

# L301-006-1001 Clinical Course

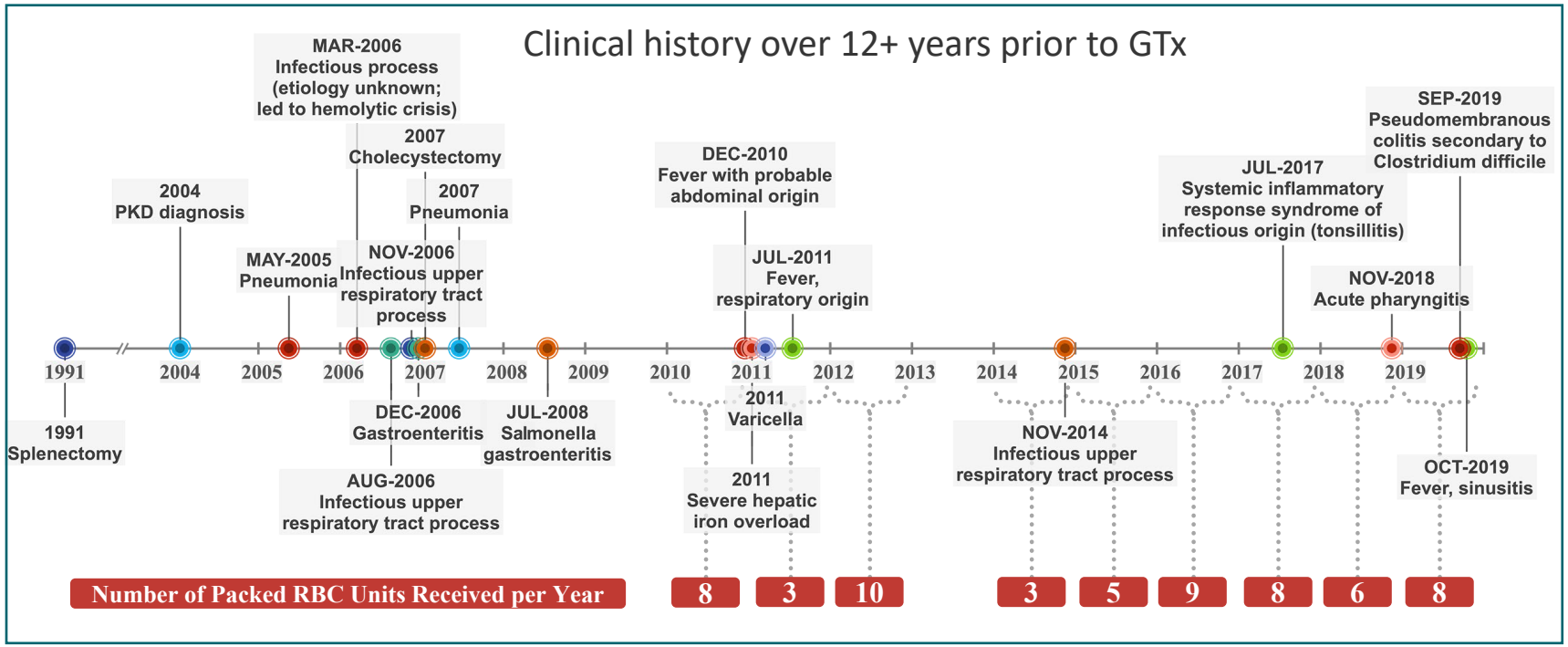
## Subject Characteristics

| Age (y) & Gender | PKD Mutation | Hemoglobin (g/dL) | Bilirubin (mg/dL) | Erythropoietin (mIU/mL) | Transfusion Requirement for 2 Years Prior to Enrollment |
|---|---|---|---|---|---|
| 31 F | c.721G>T<br>c.1529G>A | 7.4† | 13.4 | 35.6 | ~14 transfusion episodes |

† Average hemoglobin calculated over 2 years prior to study enrollment

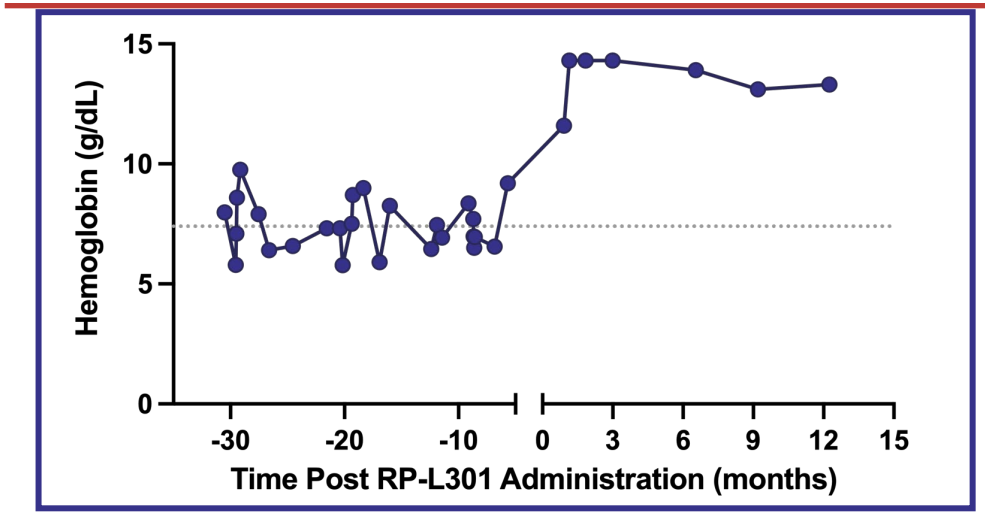
## Product Metrics

| Nucleated Cells/kg | CD34+ Cells/kg | CFCs/kg | Mean VCN: Liquid Culture |
|---|---|---|---|
| $3.9 \times 10^6$ | $3.9 \times 10^6$ | $9.2 \times 10^5$ | 2.73 |

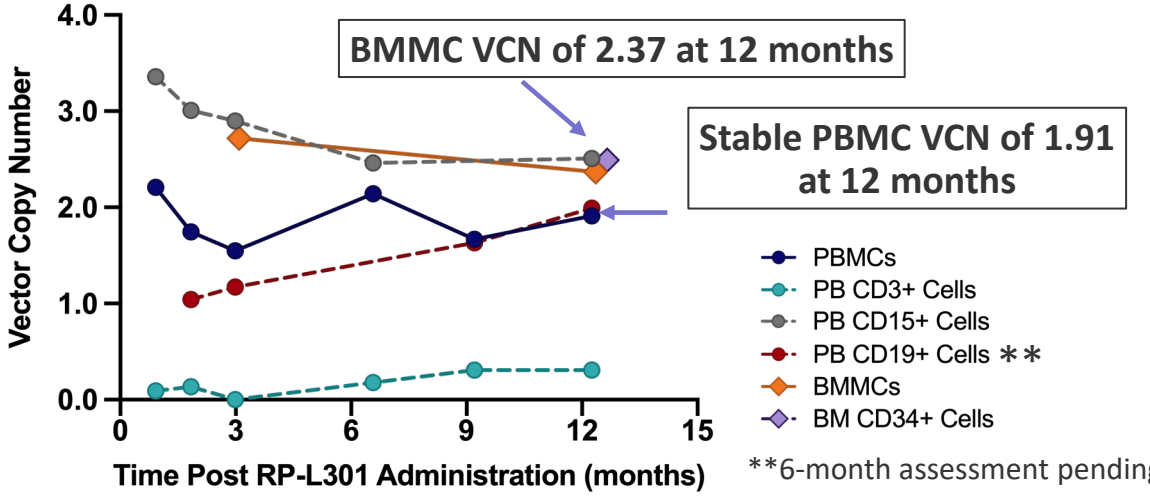



- Patient had history of multiple infections precipitating hemolytic crises & requiring multiple transfusions and hospitalizations.
- Patient had hepatic iron overload secondary to transfusions and underlying PKD.

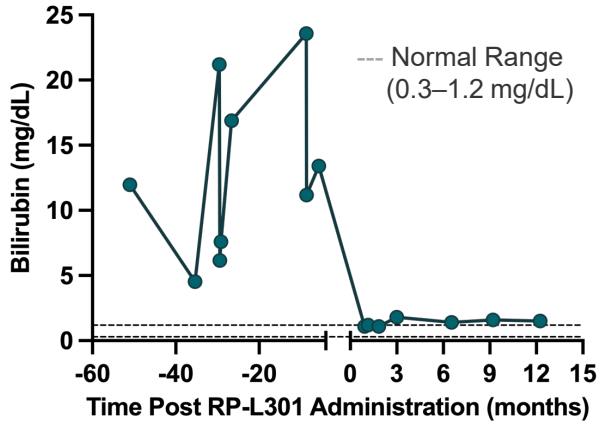
# Preliminary Efficacy Results: L301-006-1001



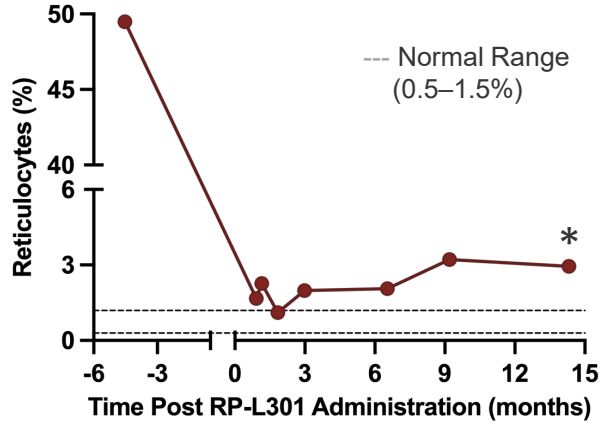

- Sustained **hemoglobin improvement from ~7.4 g/dL to 13.3 g/dL** over 12 months post-RP-L301 infusion
- No red blood cell transfusion requirements following engraftment



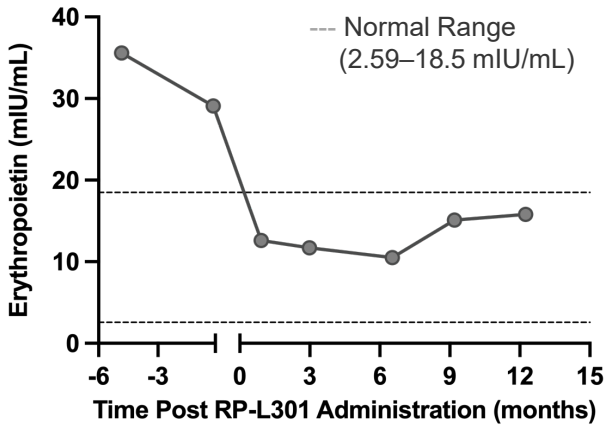

**6-month assessment pending



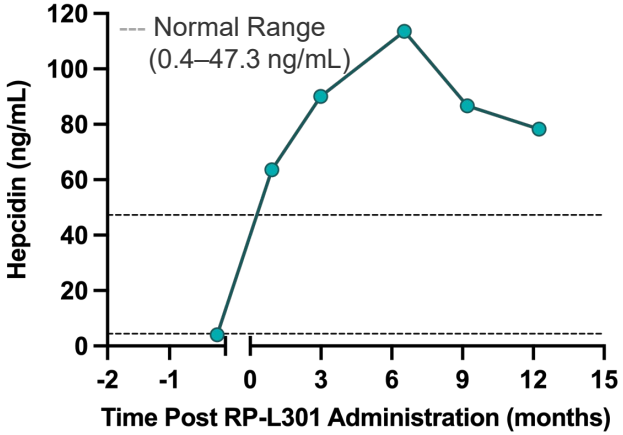

***Significant bilirubin decrease from 13.4 mg/dL to 1.5 mg/dL***




***Sustained reduction in reticulocytes***




***Continued erythropoietin normalization***




***Hepcidin increased from <4.0 ng/mL to 78.3 ng/mL***



* Reticulocytes not obtained at 12-month visit; obtained locally at ~14 months post-infusion

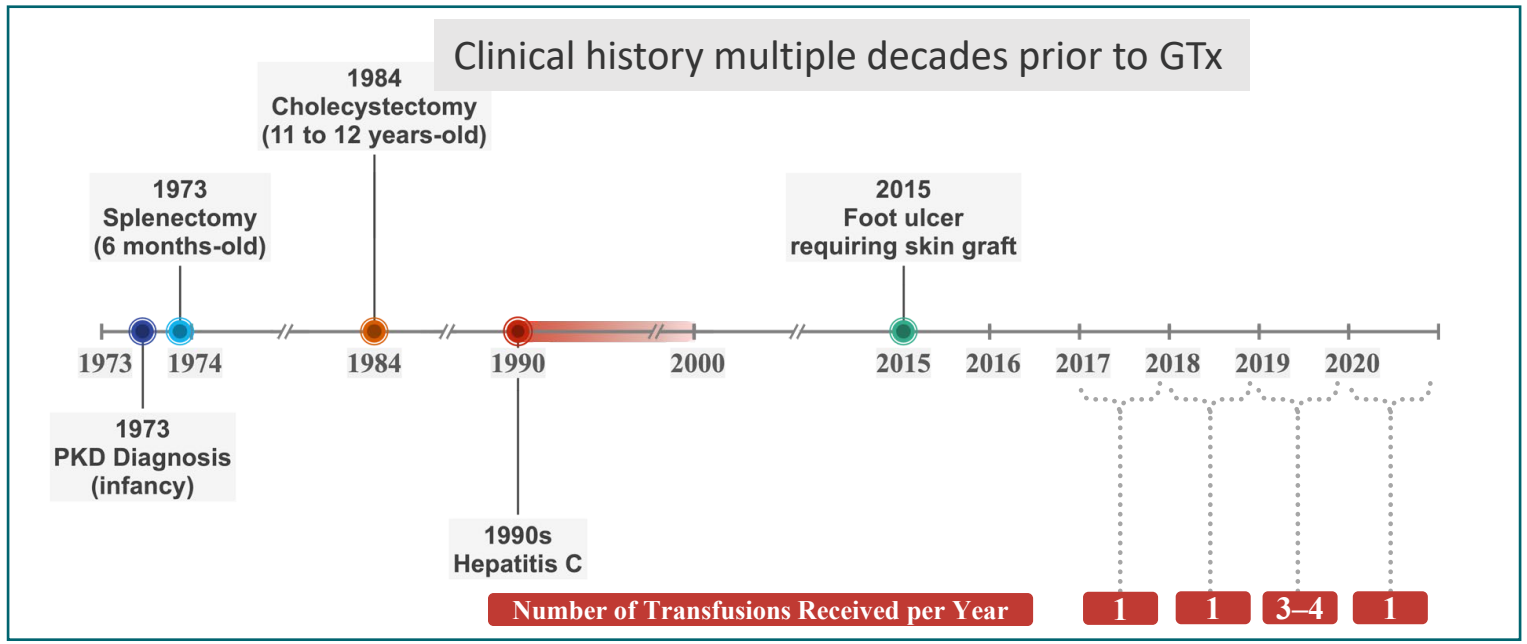
Data cut-off as of November 3, 2021

# L301-001-1002 Clinical Course

## Subject Characteristics

| Age (y) & Gender | PKD Mutation | Hemoglobin (g/dL) | Bilirubin (mg/dL) | Erythropoietin (mIU/mL) | Transfusion Requirement for 2 Years Prior to Enrollment |
|---|---|---|---|---|---|
| 47 M | c.703GGG>AGG<br>c.1047A>AA<br>c.1744CGG>AGG | 7.0‡ | 7.4 | 57.2 | ~5 transfusion episodes |

‡ Average hemoglobin calculated over 2 years prior to study enrollment

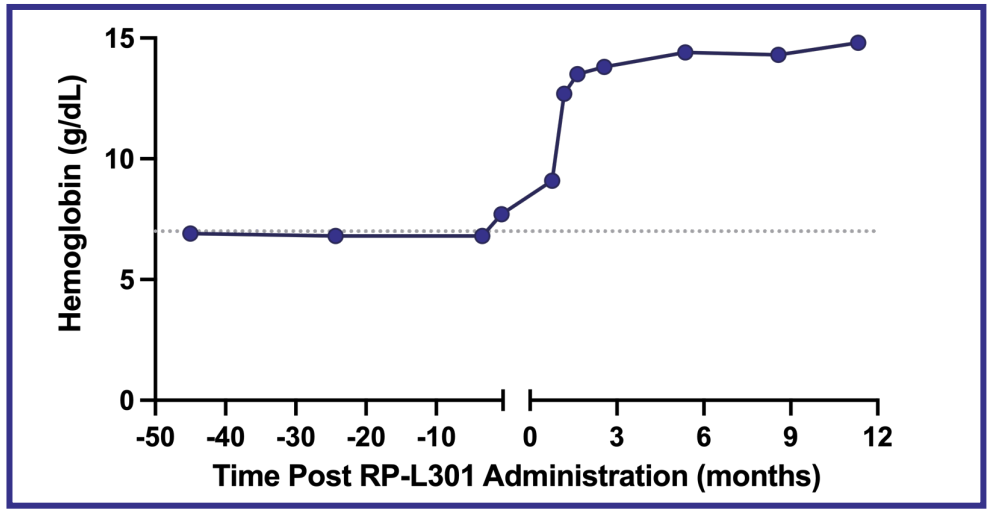



## Product Metrics

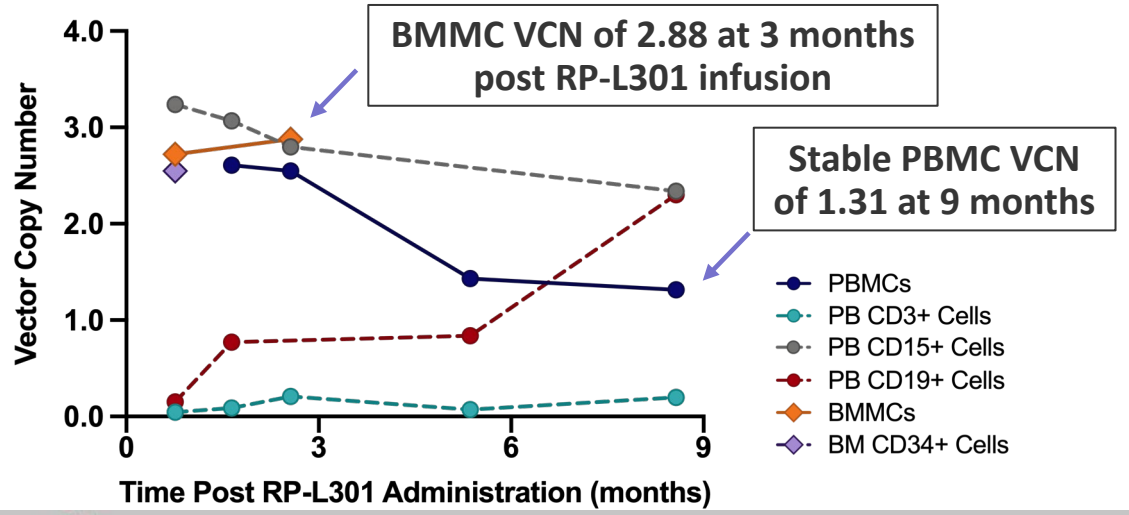
| Nucleated Cells/kg | CD34+ Cells/kg | CFCs/kg | Mean VCN: Liquid Culture |
|---|---|---|---|
| $2.4 \times 10^6$ | $2.4 \times 10^6$ | $3.4 \times 10^5$ | 2.08 |

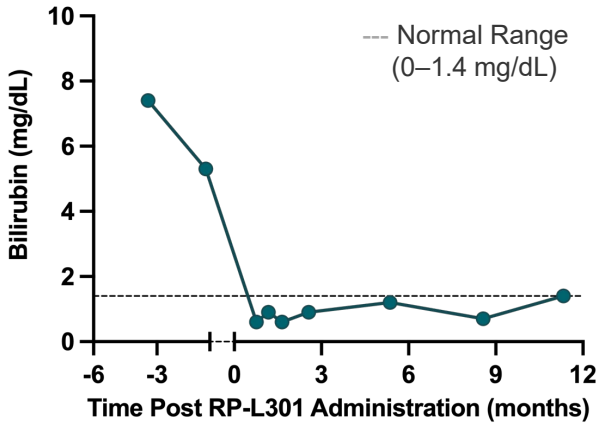
- Patient had severe anemia, but declined frequent red blood cell transfusions.
- Additional complications included liver iron overload and foot ulcer requiring skin graft.

# Preliminary Efficacy Results: L301-001-1002

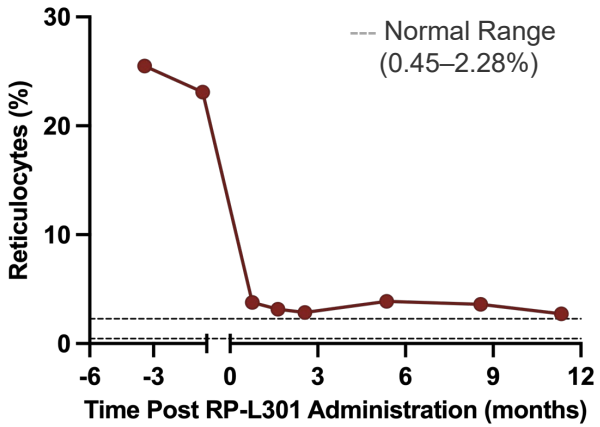



- **Hemoglobin normalized to 14.8 g/dL** at ~12 months post-rx
- No red blood cell transfusion requirements following engraftment

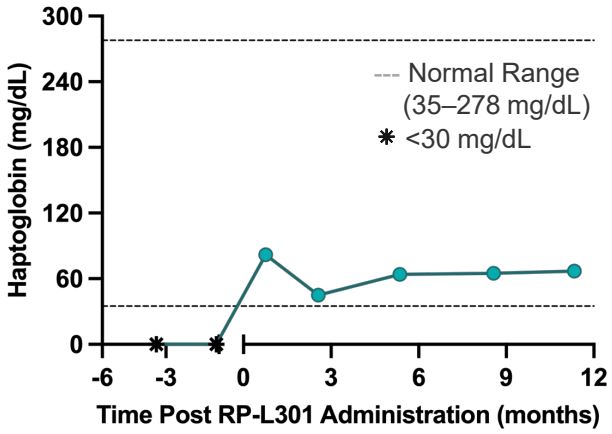


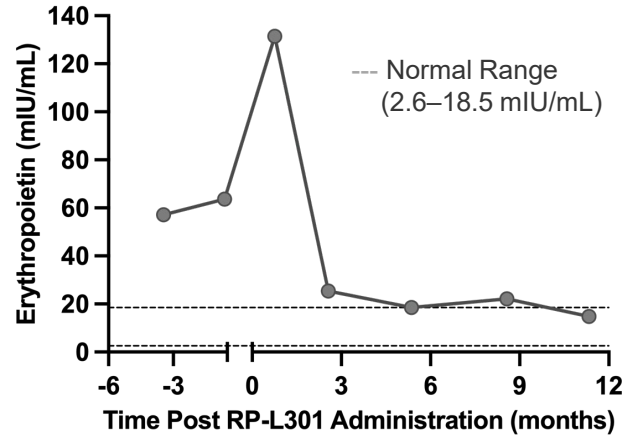

***Normalized bilirubin from 7.4 mg/dL to 1.4 mg/dL***




***Significant improvement in reticulocytes from 25.5% to 2.73%***




***Sustained haptoglobin normalization***

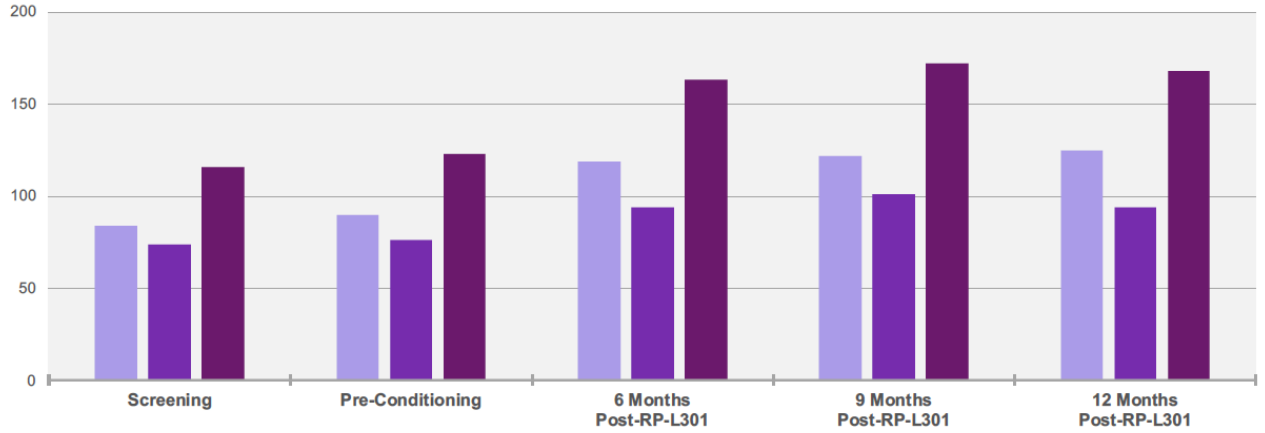



***Significant decrease in erythropoietin levels***

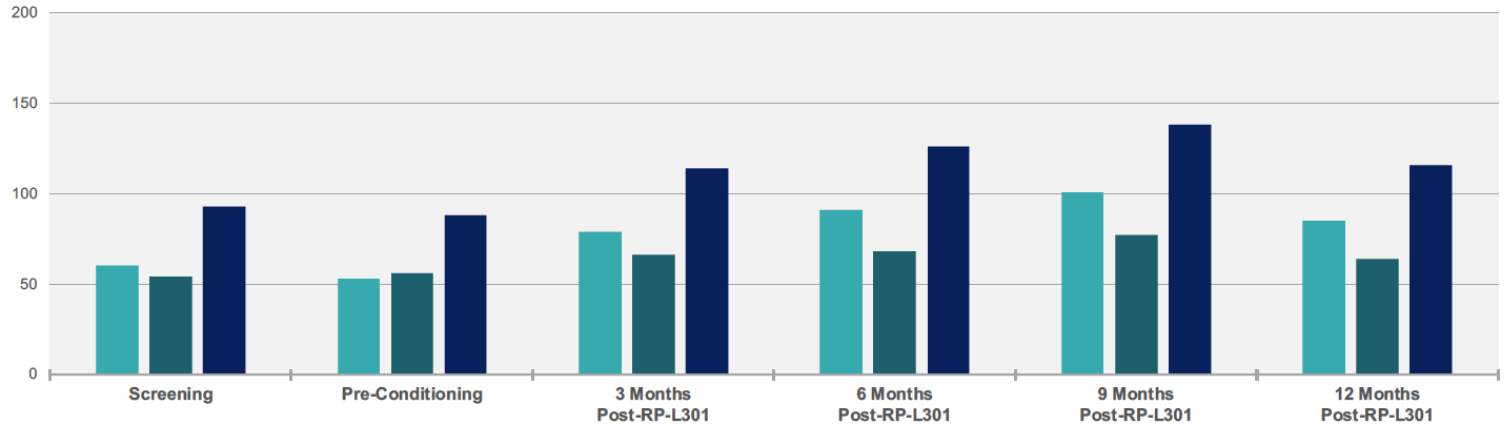
# Preliminary Results Indicate Improved Quality of Life
## during one year subsequent to RP-L301 therapy

*Functional Assessment of Cancer Therapy-Anemia (FACT-An)*

**L301-006-1001**




**L301-001-1002**




**Both patients have anecdotally reported improved quality of life (QoL) following RP-L301 administration; improved QoL has also been demonstrated by increase in FACT-An Total and component scores from baseline.**

# Conclusions

- **Hematopoietic stem and progenitor cell collection appears safe and feasible in the initial adult patients with severe PKD**

- **Safety profile of RP-L301 appears favorable**
  - Infusion well tolerated in (N=2); no IP-related serious adverse events (SAEs) at 12 months post-infusion in adult patients
  - Transient transaminase elevation seen in both subjects post conditioning and infusion with no clinical stigmata of liver injury; now resolving or resolved
  - Hematopoietic reconstitution occurred within 2 weeks post RP-L301 administration
  - Patients discharged from hospital within 1 month following RP-L301 infusion

- **Insertion site analysis for L301-006-1001 at 3 months post-RP-L301 in PB demonstrated a highly polyclonal pattern and no demonstrable insertions in proximity to potential oncogenic loci**
  - Additional ISA testing for both patients is ongoing

# Conclusions

- **Investigational product RP-L301 was successfully manufactured**
  - Liquid culture VCNs >2.0; CD34+ cell doses 2.4–3.9×$10^6$/kg

- **Preliminary efficacy has been seen in both patients at 12-months post-RP-L301 infusion as demonstrated by:**
  - Normalized hemoglobin
  - Improved hemolysis parameters
  - No red blood cell transfusion requirements following engraftment (transfusion independence)

- **Both patients have reported improved quality of life following treatment**

***Pediatric cohort is currently enrolling patients.***
***Please contact PKDclinicaltrial@rocketpharma.com for more information.***

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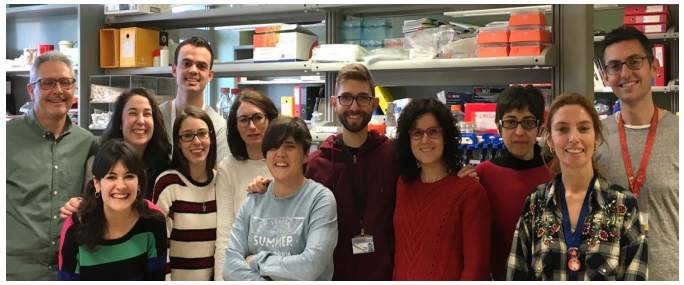

CIEMAT Team

Oscar Quintana-Bustamante, PhD

Juan Bueren, PhD

Julián Sevilla, MD, PhD

Eileen Nicoletti, MD
Gayatri R. Rao, MD, JD
Grace Choi
Miriam Zeini, PhD
Jonathan Schwartz, MD
Kinnari Patel, PharmD, MBA
Gaurav Shah, MD