Lentiviral-Mediated Gene Therapy for Adults and Children with Severe Pyruvate Kinase Deficiency: Results from an Ongoing Global Phase 1 Study

A. J. Shah, MD[1,2,3], J. L. López Lorenzo, MD[4,5], J. Sevilla, MD, PhD[6,7], S. Navarro, PhD [5,7,8], L. Llanos, MD, PhD[4,5], B. Pérez de Camino Gaisse, MD[4,5], S. Sanchez, MD[4,5], J. Zubicaray, MD, PhD[6], B. Glader, MD, PhD[2,3], M. Chien, MD[2,3], O. Quintana Bustamante, PhD[5,7,8], M. Zeini, PhD[9], G. Choi, BS[9], E. Nicoletti, MD[9], G. R. Rao, MD, JD[9], M. G. Roncarolo, MD[1,2,3], J. A. Bueren, PhD[5,7,8], J. D. Schwartz, MD[9] and J. C. Segovia, PhD[5,7,8]

[1]Center for Definitive and Curative Medicine, Stanford University, Stanford, CA; [2]Department of Pediatrics, Division of Hematology, Oncology, Stem Cell Transplantation, and Regenerative Medicine, Stanford University School of Medicine, Stanford, CA; [3]Lucile Packard Children's Hospital, Palo Alto, CA; [4]Hospital Universitario Fundación Jiménez Díaz, Instituto de Investigación Sanitaria Fundación Jiménez Díaz (IIS-FJD), Madrid, Spain; [5]Unidad Mixta de Terapias Avanzadas, Instituto de Investigación Sanitaria Fundación Jiménez Díaz (IIS-FJD), Madrid, Spain; [6]Hematología y Hemoterapia, Fundación para la investigación Biomédica, Hospital Infantil Universitario Niño Jesús (HIUNJ), Madrid, Spain; [7]Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Madrid, Spain; [8]Unidad de Innovación Biomédica, Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT), Madrid, Spain; [9]Rocket Pharmaceuticals, Inc., Cranbury, NJ

Abstract # 2138

Introduction

Pyruvate kinase deficiency (PKD) is a rare inherited hemolytic anemia caused by mutations in the *PKLR* gene which result 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 include enzyme activators or palliative therapies limited to chronic blood transfusions, iron chelation therapy, and splenectomy.
- Side effects of splenectomy in PKD include increased short- and long-term risk of disseminated infections and venous and arterial thromboembolic events.
- Allogeneic HSCT has been performed in select cases and resulted in transfusion independence; however, efficacy has been limited by significant toxicities and donor availability.

Al-Samkari H et al. N Engl J Med. 2022; 386:1432-1442.
Grace R et al. Blood. 2018; 131: 2183-2192.
Van Straaten S et al. Haematologica. 2018; 103(2): e82–e86.
Zanella A et al. Br J Haematol. 2005;130(1):11-25.

RP-L301 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 utilizing a clinically relevant PKD murine model have demonstrated safety and efficacy.
- Lentiviral gene therapy represents a potentially definitive treatment for PKD which addresses the underlying genetic defect and could ameliorate iron overload and end-organ damage.

Navarro S *et al.* Mol. Ther. – Methods Clin. Dev. 2021; 22: 350-359.
García-Gomez M *et al.* Mol. Ther. 2016; 24(7): 1187-1198.

Endpoints

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

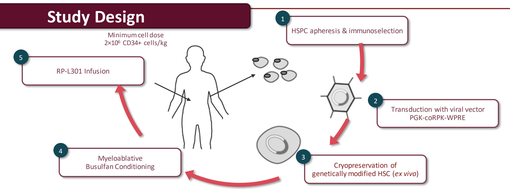
Inclusion:

- PKD diagnosis with a confirmed *PKLR* mutation
- Age: Adult cohort (N=2): ≥18 to 50 years
  Pediatric cohort (N=2-3): ≥8 to 17 years
- Severe and/or transfusion-dependent anemia
- Prior splenectomy
- 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



- Patients undergo HSPC mobilization and collection.
- Immunoselection of CD34+ cells and lentiviral-mediated *PKLR* gene transduction are conducted *ex vivo*.
- RP-L301 is infused following myeloablative busulfan conditioning

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

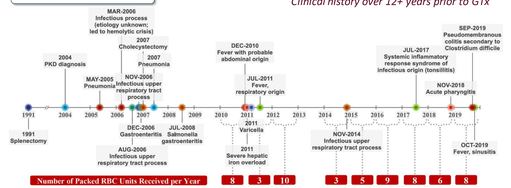
Patient Demographics, Clinical History and Investigational Product Metrics

		L301-006-1001	L301-001-1002
Patient Characteristics	Age (y) & Gender	31 F	47 M
	PKD Mutation	c.721G>T c.1529G>A	c.703GGG>AGG c.1047A>AA c.1744CGG>AGG
	Hemoglobin (g/dL)	7.4†	7.0†
	Bilirubin (mg/dL)	13.4	7.4
	Erythropoietin (mIU/mL)	35.6	57.2
	Transfusion Requirement for 2y Prior to Enrollment	~14 transfusion episodes	~5 transfusion episodes
RP-L301 Metrics	CD34+ Cells/kg	3.9×10^6	2.4×10^6
	CFCs/kg	9.2×10^5	3.4×10^5
	Mean VCN: Liquid Culture	2.73	2.08

† Average hemoglobin calculated over 2 years prior to study enrollment
CFCs: Colony forming cells, VCN: Vector copy number

L301-006-1001

Clinical history over 12+ years prior to GTx



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

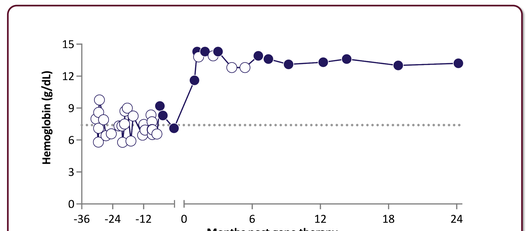
L301-001-1002

Clinical history multiple decades prior to GTx

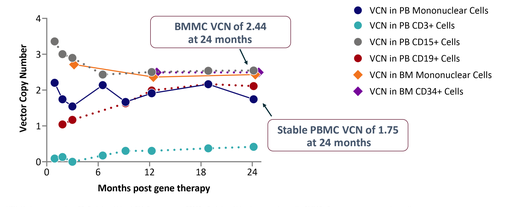
- *Patient had severe anemia, but declined frequent red blood cell transfusions.*
- *Additional complications included liver iron overload and foot ulcer requiring skin graft.*
- *Patient received prior mitapivat (AG-348) without significant hemoglobin increase.*

Interim Results

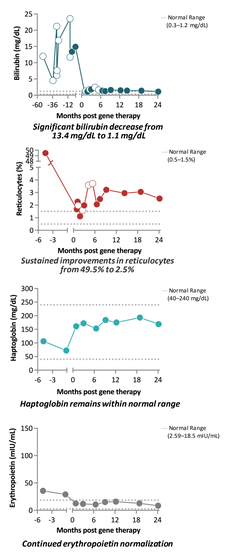
L301-006-1001



- Sustained **hemoglobin normalization from ~7.4 g/dL to 13.2 g/dL** at 24 months post-RP-L301 infusion
- No red blood cell transfusions required following engraftment



VCN: Vector copy number, PB: Peripheral blood, BM: Bone marrow, PBMCs: Peripheral blood mononuclear cells, BMMCs: Bone marrow mononuclear cells
Data cut-off: October 26, 2022; Preliminary interim results are presented from the ongoing clinical study.



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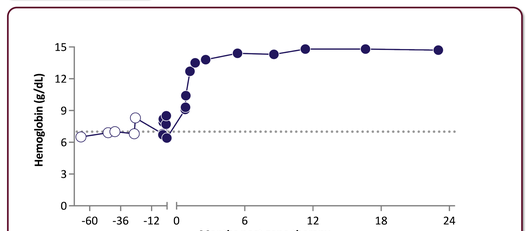
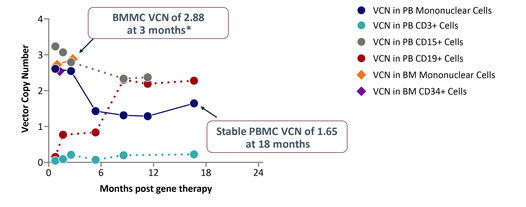
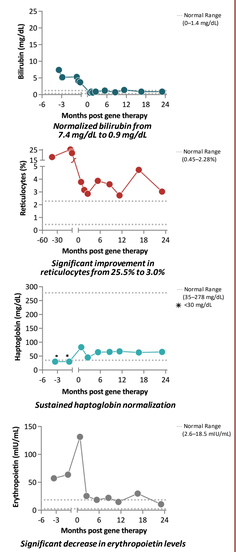


- Sustained **hemoglobin normalization from ~7.0 to 14.7 g/dL** at 24 months post-RP-L301 infusion
- No red blood cell transfusions required following engraftment



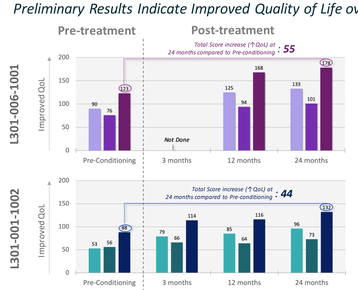
*BMMC VCN unable to be evaluated at 12 months due to technical difficulties with assay.



Quality of Life Assessments

FACT-Anemia

Preliminary Results Indicate Improved Quality of Life over 24 months subsequent to RP-L301 therapy



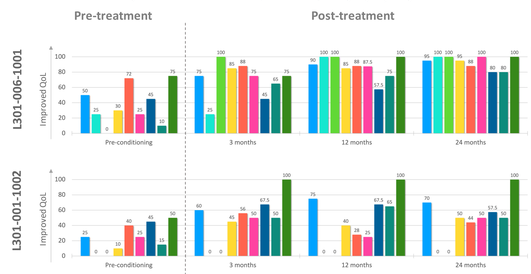
Trial Outcome Index (TOI) Score *(Score range: 0–136)*
General (G) Score *(Score range: 0–108)*
Total Score *(Score range: 0–188)*

Total Score is derived from subscales evaluating:
- Physical well-being
- Social/family well-being
- Emotional well-being
- Functional well-being
- Anemia

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.

SF-36

Preliminary Results Indicate Improved Quality of Life by SF-36 over 24 months subsequent to RP-L301 therapy



RAND 36-Item Short Form (SF-36) generic quality-of-life measures:
- Physical functioning
- Role functioning/physical
- Role functioning/emotional
- Energy/fatigue
- Emotional well-being
- Social functioning
- Pain
- General health
- Health change (previous 12 months

Substantial improvements have been reported for physical functioning, energy/fatigue, and general health components.

Previously presented data at Screening and at 6 months, 9 months, and 18 months post-gene therapy is not shown.
Data cut-off: October 26, 2022; Preliminary interim results are presented from the ongoing clinical study.

Conclusions

- **Clinical efficacy and safety data indicate that RP-L301 is a potential treatment for patients with severe PKD, including those who did not derive benefit from available therapies (i.e. mitapivat)**
- **Hematopoietic stem and progenitor cell collection appears safe and feasible in adult cohort; RP-L301 was successfully manufactured**
- **Robust and sustained efficacy in both patients at 24 months post-RP-L301 infusion demonstrated by:**
  - **Normalized hemoglobin (from baseline levels in 7.0 – 7.5 g/dL range)**
  - Improved hemolysis parameters
  - **Transfusion independence**
- **Both patients reported improved quality of life following treatment**
- **Safety Profile of RP-L301 appears highly favorable**
  - No IP-related serious adverse events (SAEs) at 24 months post-infusion
  - Transient transaminase elevation seen in both patients post conditioning and infusion with no clinical stigmata of liver injury; fully resolved
  - Neutrophil engraftment occurred within 2 weeks following gene therapy infusion
- ***Insertion site analyses in PB and BM for both adult patients for up to 12 months post-RP-L301 demonstrated highly polyclonal patterns and there has been no evidence of insertional mutagenesis***
  - Additional ISA testing for both patients is ongoing

Adult and pediatric enrollment is complete. Phase 2 trial initiation is anticipated in 2023.
Please contact PKDclinicaltrial@rocketpharma.com for more information.

Disclosures: Shah: Vertex Pharmaceuticals: Advisory Board; Bluebird Bio: Advisory Board. **Lorenzo:** There are no relationships to disclose. **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. **Navarro:** Rocket Pharmaceuticals, Inc.: Research Funding, Patents & Royalties, Equity Ownership. **Llanos:** There are no relationships to disclose. **Gaisse:** There are no relationships to disclose. **Sanchez:** There are no relationships to disclose. **Zubicaray:** Novartis: Consultancy. **Glader:** Agios Pharmaceuticals: Research Funding. **Chien:** There are no relationships to disclose. **Bustamante:** Rocket Pharmaceuticals, Inc.: Equity Ownership; Universidad Francisco de Vitoria: Teaching Activities. **Zeini:** Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. **Choi:** Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. **Nicoletti:** Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. **Rao:** Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. **Roncarolo:** There are no relationships to disclose. **Bueren:** Rocket Pharmaceuticals, Inc.: Consultancy and Research Funding. Other: Inventor on patents on lentiviral vectors filed by CIEMAT, CIBERER and fundación Jiménez Díaz, may be entitled to receive financial benefits from the licensing of such patents and receives funding for research. **Schwartz:** Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. **Segovia:** Rocket Pharmaceuticals, Inc.: Consultancy and Research Funding.