

Changing the Treatment Paradigm for Pyruvate Kinase Deficiency with Lentiviral Mediated Gene Therapy: Interim Results from an Ongoing Global Phase 1 Study

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Abstract #357

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 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 and 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.

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 performed in Dr. Segovia's lab utilizing a clinically relevant PKD murine model have demonstrated safety and efficacy.

Navarro S *et al.* Mol. Ther. – Methods Clin. Dev. 2021; 22: 350-359.
García-Gómez 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

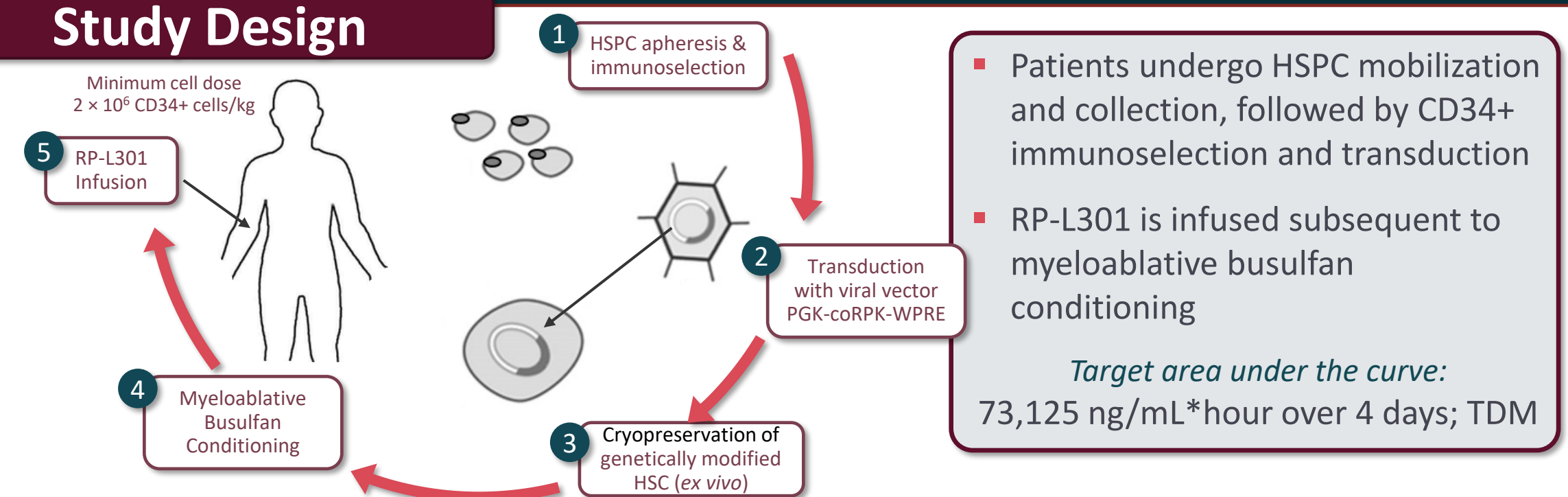
Inclusion:

- PKD diagnosis with a confirmed *PKLR* mutation
- Age: 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
- Splenectomized
- 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

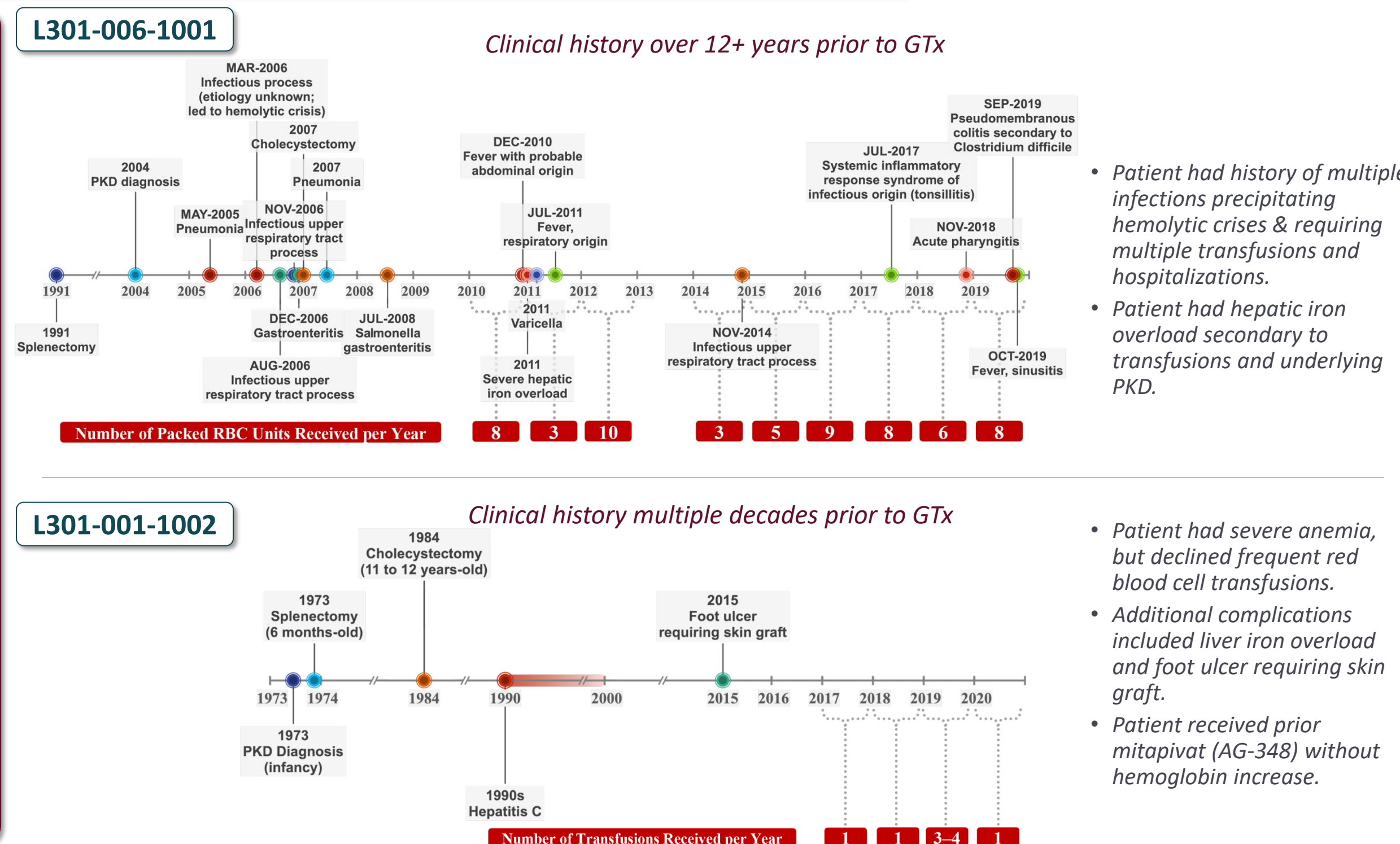
Study Design



Patient Demographics and Investigational Product Metrics

	L301-006-1001	L301-001-1002
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
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

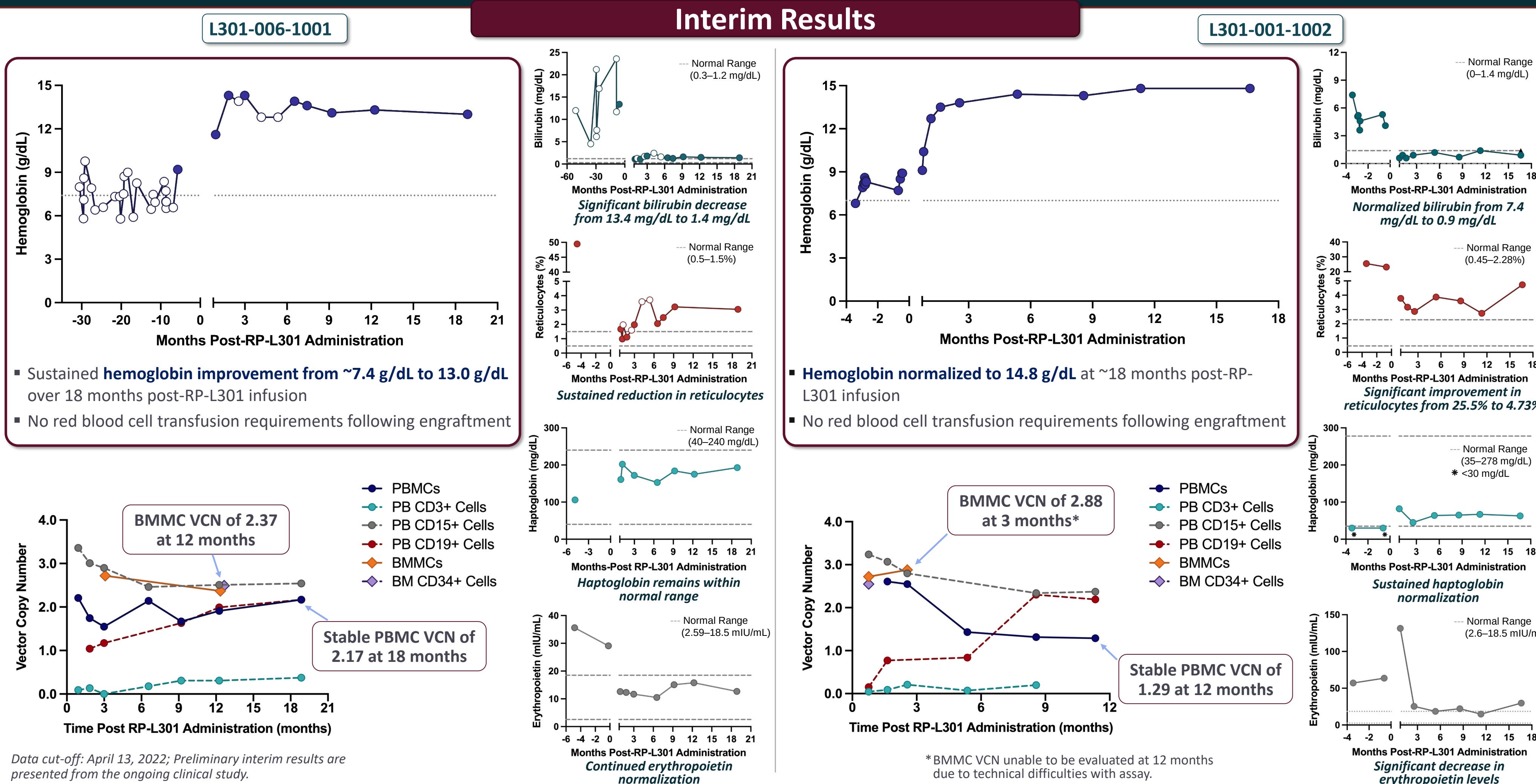


Quality of Life Assessments



Conclusions

- Hematopoietic stem and progenitor cell collection appears safe and feasible in the initial adult patients with severe PKD
- Investigational product RP-L301 was successfully manufactured
 - Liquid culture VCNs >2.0; CD34+ cell doses 2.4–3.9 × 10⁶/kg
- Robust and sustained efficacy in both patients at 18 months post-RP-L301 infusion demonstrated by:
 - Normalized hemoglobin**
 - Improved hemolysis parameters
 - No red blood cell transfusion requirements** following engraftment (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 18 months post-infusion
 - Transient transaminase elevation seen in both patients post conditioning and infusion with no clinical stigmata of liver injury; subsequently 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 no demonstrable insertions in proximity to potential oncogenic loci**
 - Additional ISA testing for both patients is ongoing



Data cut-off: April 13, 2022; Preliminary interim results are presented from the ongoing clinical study.