Lentiviral-Mediated Gene Therapy for Patients with Fanconi Anemia [Group A]: Updated Results from Global RP-L102 Clinical Trials

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26th Annual Meeting of the American Society of Gene and Cell Therapy (ASGCT)

May 18, 2023
Abstract # 217

Disclosures

- Consultant: 48 Bio, GV, Lyrik Therapeutics, Prime Medicine, Spotlight Therapeutics, Stemodontics, Teiko Bio
- Current Equity: 48 Bio, Beam Therapeutics, Decibel Therapeutics, Editas Medicine, GV, Lyrik Therapeutics, Magenta Therapeutics, Prime Medicine, Spotlight Therapeutics, Stemodontics, Teiko Bio, Divested Equity in last 24 months: Forty Seven, Inc., Global Blood Therapeutics
- Intellectual property rights: Gilead Sciences, Jasper Therapeutics, Magenta Therapeutics
- Research funding from Rocket Pharmaceuticals, Inc. Jasper Pharmaceuticals, STRM.Bio

Introduction

Fanconi anemia (FA) is a rare inherited disorder of defective deoxyribonucleic acid (DNA) repair characterized by:

- Progressive bone marrow failure (BMF); 80% of patients experience BMF within 1st decade of life
- Predisposition to hematologic malignancies and solid tumors
- Congenital abnormalities

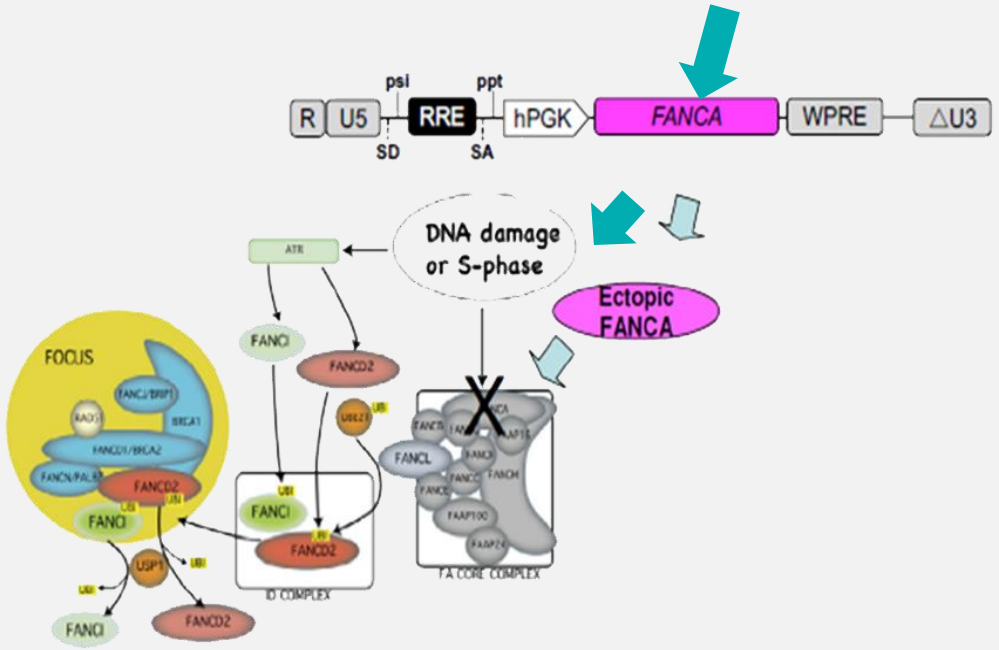
FA represents a significant unmet medical need

- FA complementation group A (FA-A) accounts for 60–70% of FA; prevalence of ~5,500–7,000 cases in US and Europe
- Allogeneic HSCT is curative of BMF, but has short- and long-term toxicities, especially for patients who do not have an HLA-identical sibling donor (~80% of patients)
  - 100-day transplant-associated mortality
  - Graft-vs-host disease (GvHD)
  - 3–4x increased risk for solid organ malignancies over high FA-associated cancer risk; ↑↑ risk with GvHD
  - HSCT-associated coronary artery disease, musculoskeletal & neurocognitive dysfunction, endocrinopathies

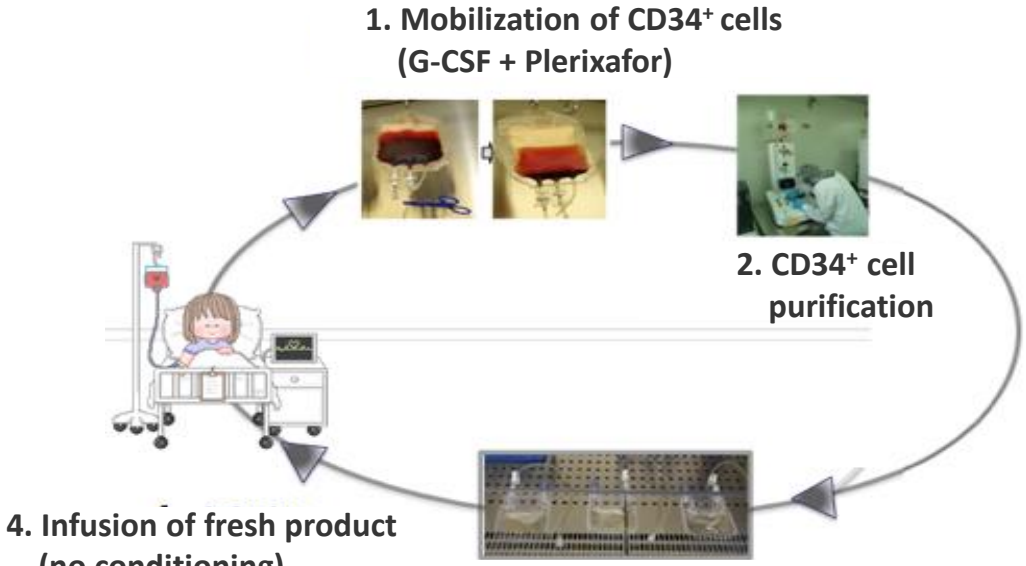
Anur P *et al*. Bone Marrow Transplant 2016; 51(7): 938-944.
Ebens C *et al*. Biol Blood Marrow Transplant 2018; 24(4): 765-771.
Guardiola P *et al*. Blood 2004; 103(1): 73-77.
Mehta P *et al*. Blood 2017; 129(16): 2308-2315.

RP-L102 Rationale

- Insertion of a functional *FANCA* gene into autologous FA-A CD34+ cells confers resistance to DNA-damage & provides proliferative advantage to modified cells
- Enables engraftment in the absence of conditioning as demonstrated in the FANCOLEN-I trial



Schematic of Product Manufacture and Treatment



Patients undergo hematopoietic stem cell (HSC) mobilization and collection, followed by CD34+ immunoselection, transduction, and subsequent infusion *without conditioning*.

Río P *et al*. Nat Med 2019; 25:1396-1401.

Global RP-L102 Studies

Key Eligibility Criteria

Inclusion:

- FA complementation group A
- Minimum age: 1y
- Maximum age: US Ph 1 (12y); US Ph 2 (none); EU Ph 2 (17y)
- BM CD34+ cell concentration: ≥30/µL (from aspirate)

Exclusion:

- Available & eligible HLA-identical sibling donor
- MDS or leukemia (including associated cytogenetic abnormalities)
- Mosaicism with stable/improved blood counts

Endpoints

Efficacy:

Phenotypic correction: Increased resistance of BM cells to DNA-damaging agent mitomycin-C (MMC)

Engraftment: Peripheral blood (PB) and BM vector copy number (VCN)

Clinical response: Prevention of BMF (stabilization or increase in blood [PB] counts)

Safety of RP-L102

12 Patients Treated with ≥ 1 year of Follow Up: Demographics and Investigational Product Metrics

Patient #	Age at Enrollment (years)	Follow Up (months)	CD34+ Cell Dose (cells/kg)	CFCs/kg	Mean VCN: Liquid Culture	Mean VCN: CFCs	Transduction Efficiency in CFCs (%)	CFC Survival MMC 10nM (%)
1 (1001)	5	48	2.0×10^5	5.2×10^4	2.08	0.62**	67	33
2 (1002)	6	18†	3.7×10^5	5.0×10^4	2.21	0.92**	72	47
3 (2004)	3	42	4.8×10^5	1.3×10^5	1.70	0.73	100	63
4 (2008)	2	32	3.2×10^6	5.5×10^5	1.65	1.56	97	63
5 (2009)	3	28‡	1.9×10^6	3.1×10^5	2.16	0.76	61	45
6 (2010)	3	28	4.1×10^6	n/a	0.62	n/a	n/a	n/a
7 (2011)	5	28	2.8×10^6	n/a	1.46	n/a	n/a	n/a
8 (2014)	6	28	5.4×10^5	3.6×10^4	3.68	1.93	87	31
9 (2016)	2	24	3.0×10^5	2.5×10^4	1.96	0.64	88	64
10 (2021)	2	18	2.3×10^6	4.3×10^5	1.55	1.97	78	38
11 (2023)	5	15	2.5×10^5	2.8×10^4	1.70	2.16	87	50
12 (2024)	1	12	1.8×10^6	1.7×10^5	1.69	1.91	88	93

All patients ≤ 6 years old at enrollment

12 patients have ≥ 12 months of follow-up

Trial enrollment is complete; 2 additional patients recently treated

Median Values

VCN (liquid culture): 1.7
VCN (CFC): 1.24
Transduction efficiency: 87%
CFC MMC-resistance: 48.5%

** Mean CFC VCN was assessed from a cryopreserved drug product sample

† Patient withdrawn from RP-L102 study at 18 months post-RP-L102 infusion; received successful allogeneic HSCT for BMF. Safety follow up continues on LTFU study.

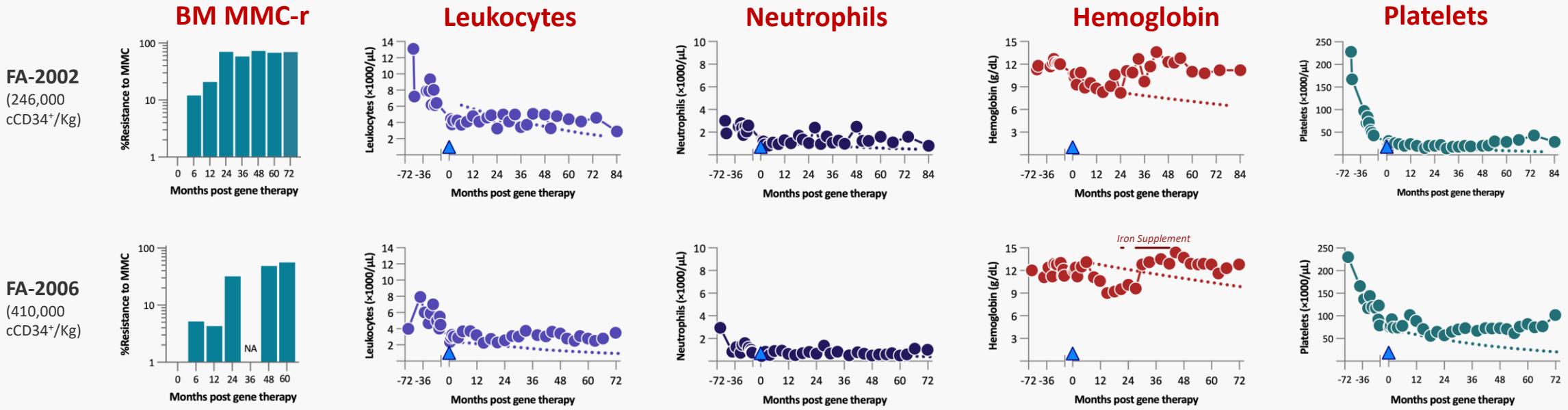
‡ Patient withdrawn from RP-L102 study at 28 months post-RP-L102 infusion; received successful allogeneic HSCT for NHL. Safety follow up continues on LTFU study.

Abbreviations: BMF: Bone marrow failure; CFC: colony-forming cell; HSCT: Hematopoietic stem cell transplantation; LTFU: Long-term follow-up; m: months; MMC: Mitomycin-C; n/a: not available; NHL: Non-Hodgkin Lymphoma; VCN: vector copy number

Data cut-off: April 17, 2023; Preliminary interim results are presented from the ongoing clinical studies.

MMC Resistance in Bone Marrow Colony-Forming Cells is Associated with Long-term Hematologic Stability

FANCOLEN-I (investigator-initiated) long-term follow-up:



≥ 20% BM CFC MMC resistance is associated with long-term hematologic stability (up to 7 years post-gene therapy) as demonstrated by FANCOLEN-I patients FA-2002 and FA-2006

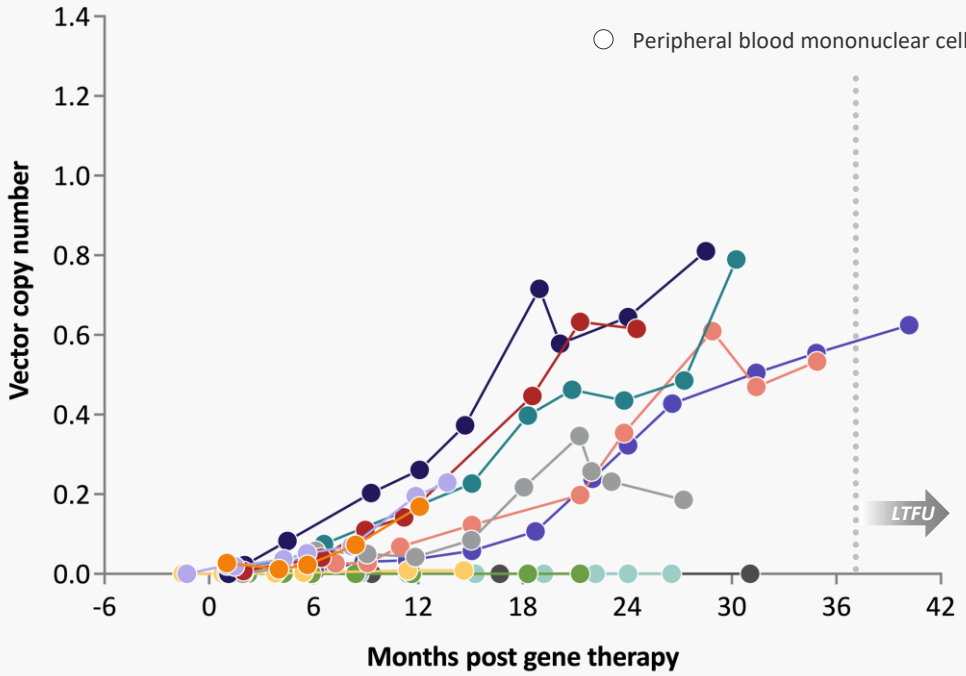
- FA-2002 has had concomitant sustained blood count stabilization, with trends suggesting increases in hemoglobin and platelets after 24 and 30 months, respectively
- FA-2006 has had blood count stabilization with hemoglobin improvement after 24 months

Dotted lines indicate projected blood count decreases based on natural history evaluation from n=139 FA-A patients (IFAR registry, data on file). The regression models fit to estimate % of change used only visits at which patient age was less than 12 years old.

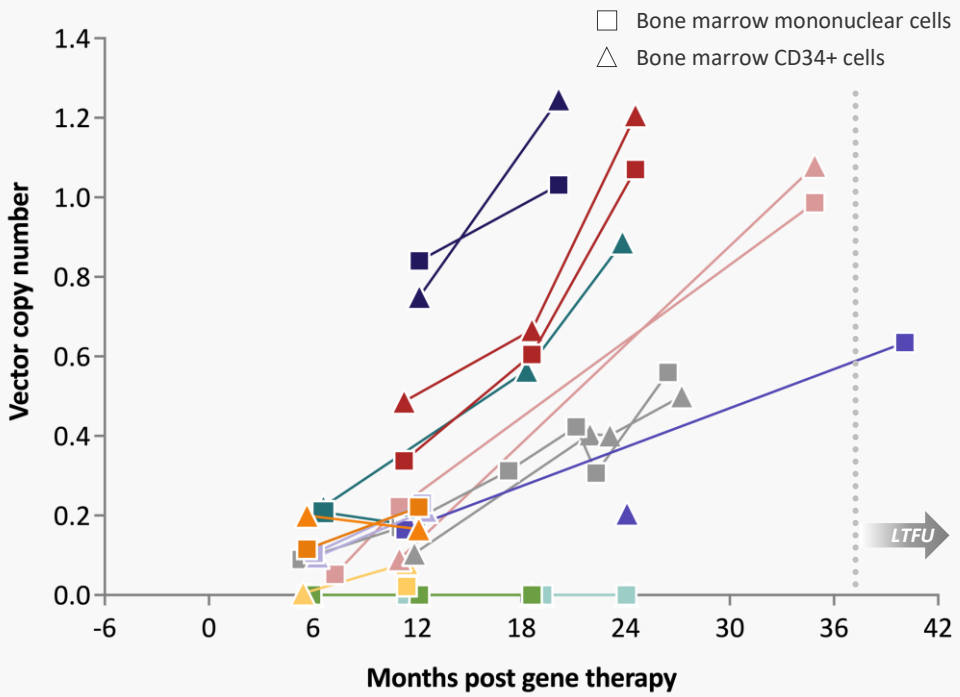
Data cut-off April 17, 2023; Preliminary interim results are presented from the on-going clinical trial.

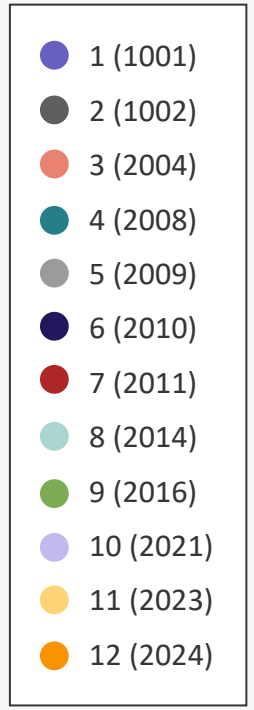
Progressively Increasing and Sustained Genetic Correction in 8 of 12 Patients at ≥ 1 year post-RP-L102

Peripheral Blood



Bone Marrow



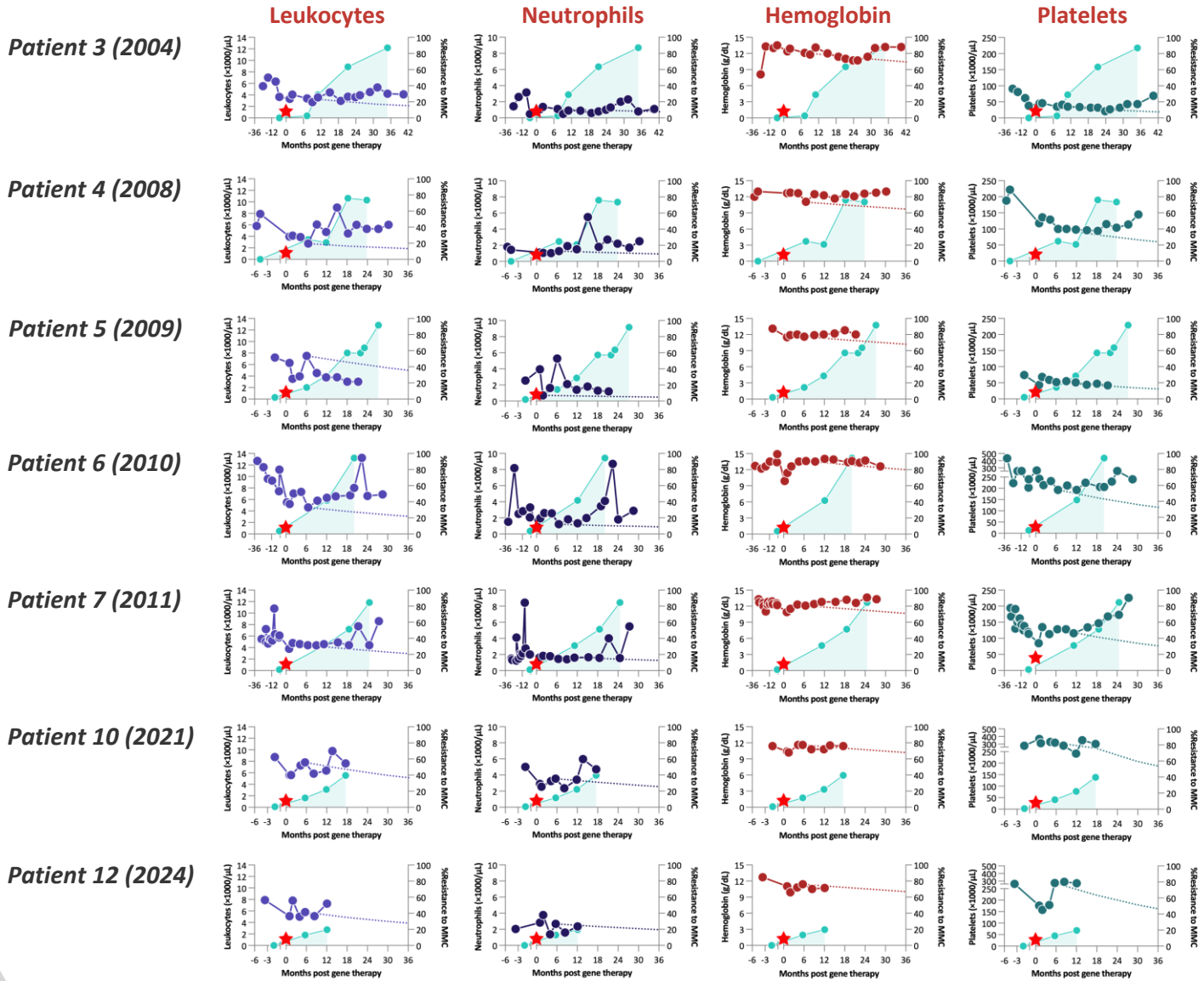


Progressive increases in gene markings in PB and BM in 8 patients

Vector copy number in bone marrow not available at some stipulated time points due to insufficient sample to perform assay

Data cut-off: April 17, 2023; Preliminary interim results are presented from the ongoing clinical studies.

Sustained BM CFC MMC-Resistance in 7 of 12 Patients Is Associated with Hematologic Stabilization at ≥ 1 year post-RP-L102



- Development of BM CFC MMC resistance ≥20% within 1–2 years post-RP-L102 is associated with hematologic stabilization for up to 3.5 years following gene therapy
- Patients have not required blood transfusions, growth factors, or allogeneic HSCT for BMF

- RP-L102 Infusion
- % Resistance to [10nM] MMC in BM CFCs
- Leukocytes (×1000/µL)
- Neutrophils (×1000/µL)
- Hemoglobin (g/dL)
- Platelets (×1000/µL)

Dotted lines indicate projected blood count decreases based on natural history evaluation from n=139 FA-A patients (IFAR registry, data on file).
The regression models fit to estimate % of change used only visits at which patient age was less than 12 years old.

Abbreviations: BM: Bone marrow; BMF: Bone marrow failure; CFC: Colony-forming cell (progenitor); HSCT: Hematopoietic stem cell transplantation; MMC: Mitomycin-C

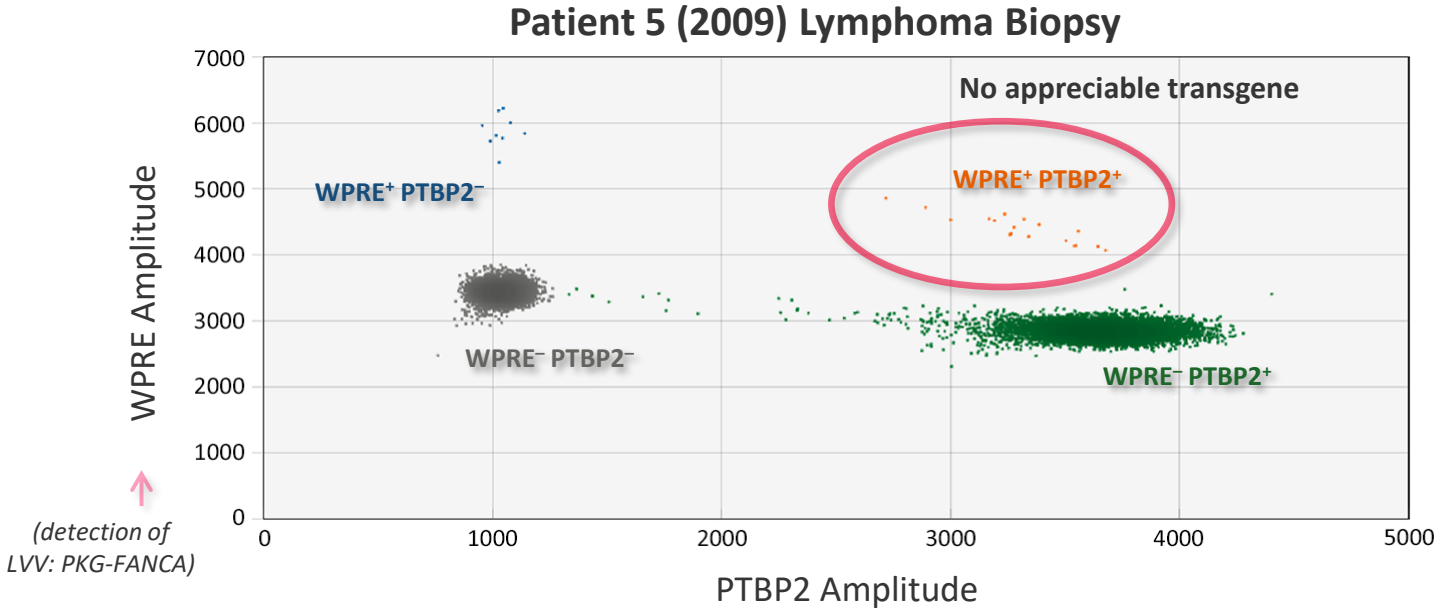
Data cut-off: April 17, 2023; Preliminary interim results are presented from the ongoing clinical studies. Hematology up to the most recent visit prior to lymphoma diagnosis/therapy is shown for Patient 5 (2009).

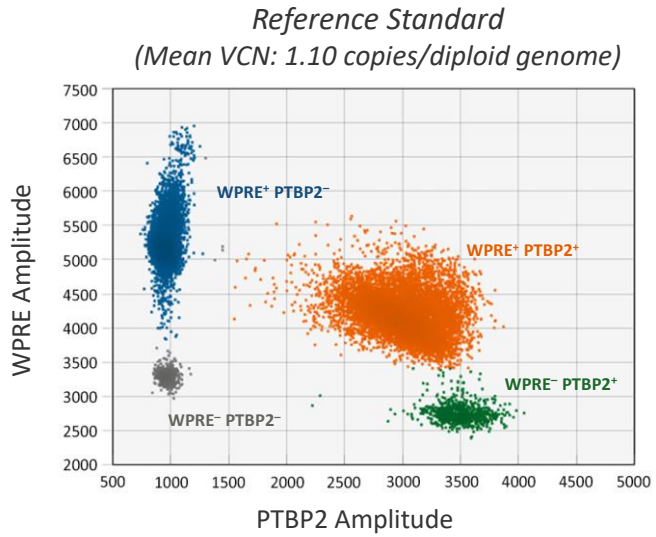
RP-L102 Safety Profile Appears Highly Favorable

- Patients are treated without antecedent conditioning and attendant risks
- Gene therapy does not preclude subsequent allogeneic HSCT if necessary
- RP-L102 related SAE: 1 patient experienced a Grade 2 transient infusion-related reaction; resolved without any additional clinical sequelae
- Unrelated adverse event: Patient 5 (2009) was diagnosed with T cell lymphoblastic lymphoma approximately 22 months post-infusion which was determined to be **unrelated to RP-L102**. Tolerated chemotherapy and subsequent allo-HSCT with minimal toxicities.

Unrelated Adverse Event: T cell lymphoblastic lymphoma

Lymphoma biopsy specimen demonstrated no appreciable LV integration
Mean VCN: 0.00314 copies/diploid genome



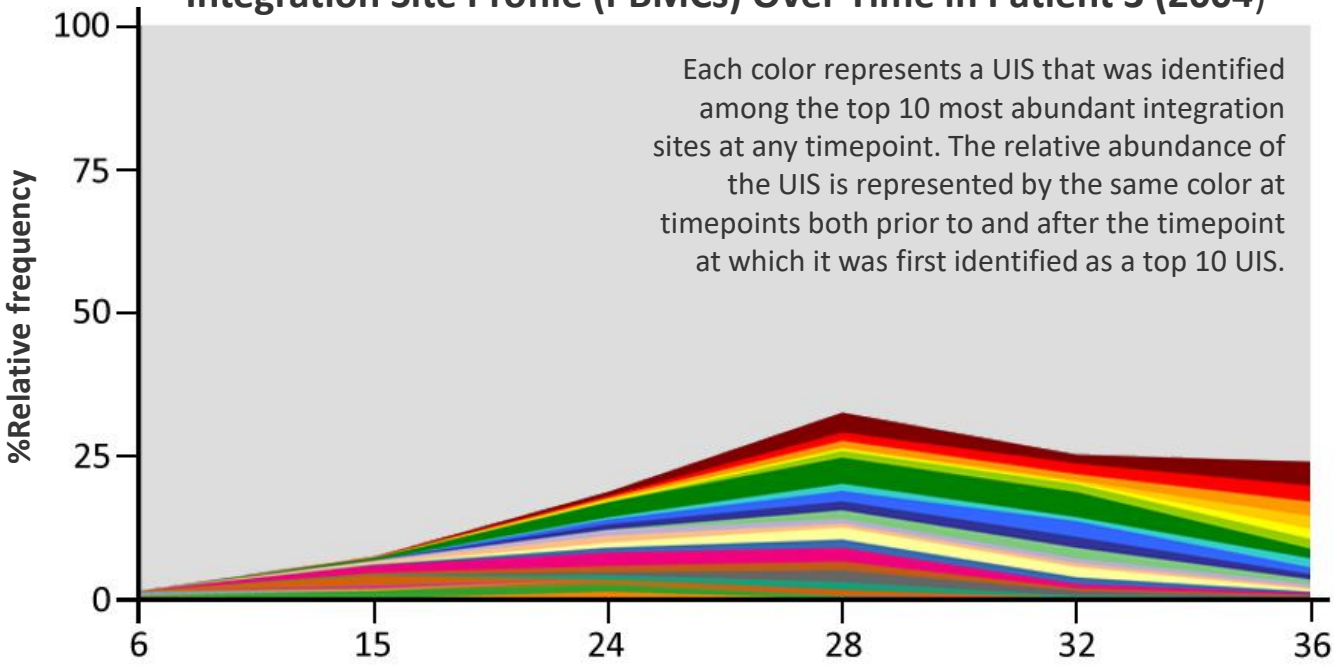


- **PB and BM mononuclear cell VCN were 0.2573 and 0.4227, respectively at time of diagnosis** (approximately 80- to 130-fold > tumor VCN)
- **Comprehensive genetic profiling revealed mutations consistent with T cell lymphoid malignancies including:**
  - *NOTCH1* deletion exons 16–27, I1680N
  - *CDKN2A/B* CDKN2B loss, CDKN2A loss
  - *CTCF* R129*
  - *DNM2* inversion exons 11–12
  - *PHF6* Y325fs*26
- Chemotherapy for T-ALL was tolerated well with minimal toxicities and clinical complete response; underwent successful allo-HSCT.
- Negligible VCN in lymphoma was likely result of blood cells within tumor specimen

Data cut-off: April 17, 2023; Preliminary interim results are presented from the ongoing clinical studies.

Polyclonal Insertion Patterns Identified Post RP-L102 Therapy
In Absence of Conditioning

Integration Site Profile (PBMCs) Over Time in Patient 3 (2004)



Month 6		Month 15		Month 24		Month 28		Month 32		Month 36	
%Relative Frequency	Closest Gene	%Relative Frequency	Closest Gene	%Relative Frequency	Closest Gene	%Relative Frequency	Closest Gene	%Relative Frequency	Closest Gene	%Relative Frequency	Closest Gene
0.2	MPHOSPH9*	1.6	SKAP2*	2.7	VARS1*	4.6	VARS1*	4.4	VARS1*	4.2	METTL16*
0.2	MRPS27*	1.4	OPRL1*	2.4	SLC2A5	3.5	METTL16*	2.7	MSH5*	2.8	KIF1C*
0.2	SATB1*	1.3	SLC2A5	1.3	SKAP2*	2.4	SLC2A5	1.9	GPATCH8*	2.5	NKTR*
0.2	IQCB1*	0.5	RAB40C*	1.2	RAB40C*	2.1	GPR141	1.9	KIF1C*	2.3	CTNNBIP1*
0.1	PPP6R2*	0.5	NAA25	1.2	OPRL1*	2.0	ATP6V0A2*	1.9	SPATS2*	1.8	AKAP8L*
0.1	NBEAL1*	0.4	VARS1*	1.1	ANKRD11	1.8	MSH5*	1.8	GPR141	1.7	GTF2I*
0.1	OPRL1*	0.3	ANKRD11	1.0	GALE	1.6	GPATCH8*	1.5	METTL16*	1.7	VARS1*
0.1	TRIM52-AS1	0.3	ACACA*	0.9	GPATCH8*	1.5	ANKRD11	1.4	GTF2I*	1.6	ZMYM4*
0.1	NEDD4*	0.2	MAP3K1~*	0.9	GNG7*	1.5	KIF1C*	1.2	PPIL4	1.1	MSH5*
0.1	PACS2*	0.2	TAOK1*	0.9	PPIL4	1.5	SPATS2*	1.1	NKTR*	0.9	GPATCH8*
PBMC VCN: 0.026		PBMC VCN: 0.123		PBMC VCN: 0.354		PBMC VCN: 0.610		PBMC VCN: 0.469		PBMC VCN: 0.533	

PBMC ISA % = [% contribution to all UIS] × [VCN] if PB VCN <1.0 OR
= [% contribution to all UIS] = [1.0] if PB VCN ≥1.0

* Integration within a transcription unit
~ Integration within 50 kb of proto-oncogene

No signs of bone marrow dysplasia, clonal dominance or insertional mutagenesis to date in RP-L102 treated patients

Integration site analysis in PBMCs have demonstrated predominantly polyclonal insertional patterns for up to 36 months in 8 evaluable patients †

† ISA evaluated if PBMC VCN ≥0.02

Data cut-off: April 17, 2023; Preliminary interim results are presented from the ongoing clinical studies.

Conclusions

RP-L102 is a potentially curative therapy to prevent FA-related BMF, which can be administered without a suitable allogeneic donor or transplant related toxicities.

- **Efficacy: Observed in 7 of 12 evaluable patients with ≥ 1 year of follow-up in the *absence of conditioning***
  - Phenotypic correction as demonstrated by sustained increase in BM CFC MMC resistance
  - Concomitant genetic correction indicating engraftment of product
  - Hematologic stabilization
- **Safety: Infusion is well tolerated with a highly favorable safety profile**
  - SAEs: 1 patient experienced an RP-L102 infusion-related reaction (transient, Grade 2)
  - 1 patient developed T-cell lymphoblastic lymphoma determined to be unrelated to RP-L102
  - No signs of bone marrow dysplasia, clonal dominance or insertional mutagenesis related to RP-L102
  - Polyclonal integration patterns identified in each of the 7 patients with phenotypic, genetic and hematologic evidence of engraftment

Phase 2 Pivotal studies completed

Engagement with Global Health Authorities regarding Product Registration ongoing

** Efficacy in ≥5 patients (observed >1 year post rx) required to reject null hypothesis*

Acknowledgements

Hospital Infantil Universitario Niño Jesús
SaludMadrid
Comunidad de Madrid

Julián Sevilla, MD, PhD
Josune Zubicaray, MD, PhD
Elena Sebastian, MD, PhD

ciberer
Centro de Investigación Biomédica en Red
Enfermedades Raras
Ciemat

Hospital Universitario
Fundación Jiménez Díaz
Grupo quirónsalud

Juan Bueren, PhD
Paula Río, PhD
Susana Navarro, PhD

Stanford Children's Health
Lucile Packard Children's Hospital Stanford

Maria Grazia Roncarolo, MD, PhD
Rajni Agarwal, MD

UCL
GREAT ORMOND STREET INSTITUTE OF CHILD HEALTH

Claire Booth, MBBS, PhD, MSc, FRCPCH
Philip Ancliff, MA, MRCP, MRCPath
Adrian J. Thrasher, MBBS, PhD, FMedSci
Kritika Chetty, MBBS
Grainne O'Toole
Jinhua Xu-Bayford

John E. Wagner, MD
Margaret MacMillan, MD
Cindy Eide, MS

MHH
Medizinische Hochschule Hannover

Michael Rothe, PhD
Antonella Lucía Bastone, PhD
Axel Schambach, PhD

rocket pharma

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

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