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

J Sevilla MD, PhD[1,2], A Czechowicz MD, PhD[3,4,5], C Booth MBBS, PhD[6], R Agarwal MD[3,4,5], J Zubicaray MD, PhD[1], P Río PhD[2,7,8], S Navarro PhD[2,7,8], K Chetty, MBBS[6], G O'Toole [6], J Xu-Bayford[6], P Ancliff MA, MRCP, MRCPath[6], E Sebastián MD, PhD[1], G Choi BS[9], M Zeini PhD[9], E Nicoletti MD[9], JE Wagner MD[10], GR Rao MD, JD[9], A Thrasher MBBS, PhD[6], JD Schwartz MD[9], MG Roncarolo MD* [3,4,5], JA Bueren PhD*[2,7,8]

[1]Hematología y Hemoterapia, Fundación para la investigación Biomédica, Hospital Infantil Universitario Niño Jesús (HIUNJ), Madrid, Spain; [2]Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Madrid, Spain; [3]Center for Definitive and Curative Medicine, Stanford University, Stanford, California, USA; [4]Department of Pediatrics, Stanford University School of Medicine, Stanford, California, USA; [5]Lucile Packard Children's Hospital, Palo Alto, California, USA; [6]UCL Great Ormond Street Institute of Child Health, London, UK; [7]Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT), Madrid, Spain; [8]Instituto de Investigación Sanitaria Fundación Jiménez Díaz (IIS-FJD), Madrid, Spain; [9]Rocket Pharmaceuticals, Inc., Cranbury, New Jersey, USA; [10]University of Minnesota, Minneapolis, Minnesota, USA ***authors contributed equally to this work**

Abstract # P139

Introduction

Fanconi anemia (FA) is a rare inherited DNA repair disorder characterized by:
- Progressive bone marrow failure (BMF); 80% in first decade
- Predisposition to hematologic malignancies and solid tumors
- Congenital abnormalities

FA complementation group A (FANCA) accounts for 60–70% of FA. Estimated US+EU prevalence for FA ~4,000 patients.

Allogeneic hematopoietic stem cell transplant (alloHSCT) is frequently curative of FA-associated BMF. However, its utilization & efficacy are limited by:
- donor availability
- graft-versus-host disease (GVHD)
- acute & long-term toxicities including increased solid tumor risk (particularly in patients with chronic GVHD)

Study Endpoints

Efficacy:
Engraftment: Peripheral blood (PB) and bone marrow (BM) vector copy number (VCN)
Phenotypic correction: Increased resistance of BM and PB cells to DNA-damaging agents mitomycin-C (MMC) and diepoxybutane (DEB)
Clinical response: Prevention of BMF (stabilization or increase in PB counts)
Safety of RP-L102

Key Eligibility Criteria

Inclusion criteria:
- 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 CD34+ cells/µL (from aspirate)
- *US Ph 1 only : At least 1 hematologic parameter (Hb, ANC, or Plt) below lower limit of normal*

Exclusion criteria:
- Available and eligible HLA-identical sibling donor
- Lansky Play Score ≤60%
- MDS or leukemia (including associated cytogenetic abnormalities)
- Mosaicism with stable/improved blood counts

RP-L102 Rationale and Study Design

- Insertion of a functional *FANCA* gene into autologous FA-A HSPCs confers resistance to DNA-damage and provides proliferative advantage to modified cells and their progeny
- Enables engraftment in the absence of conditioning as demonstrated in FANCOLEN-I (Río P, *et al*. Nat Med 2019; 25:1396-1401)

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

RP-L102 Safety Profile Appears Highly Favorable

- Patients are treated without antecedent conditioning and attendant risks
- No signs of bone marrow dysplasia, clonal dominance or insertional mutagenesis related to RP-L102
- Gene therapy does not preclude subsequent allogeneic HSCT if necessary
- Patient 2 (1002) had progressive BMF and underwent successful allo-transplant at 18 months post-RP-L102 administration
- 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.

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

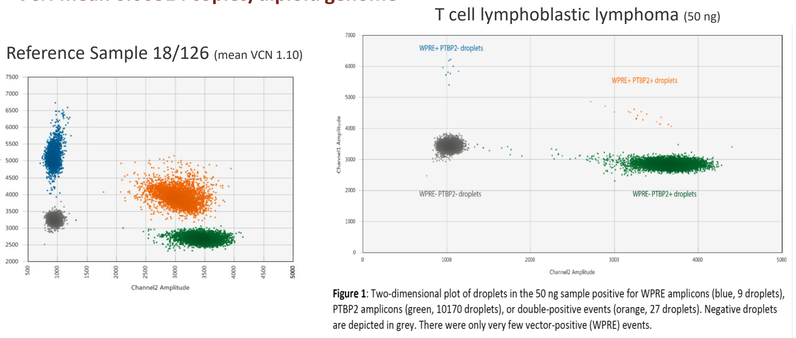


Figure 1: Two-dimensional plot of droplets in the 50 ng sample positive for WPRE amplicons (blue, 9 droplets), PTBP2 amplicons (green, 10170 droplets), or double-positive events (orange, 27 droplets). Negative droplets are depicted in grey. There were only very few vector-positive (WPRE) events.

- **PBMC and BMMC 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
- **Induction chemotherapy for T-cell lymphoblastic lymphoma was tolerated well with clinical complete response**

Data cut-off: May 11 2022; Preliminary interim results are presented from the ongoing clinical studies.

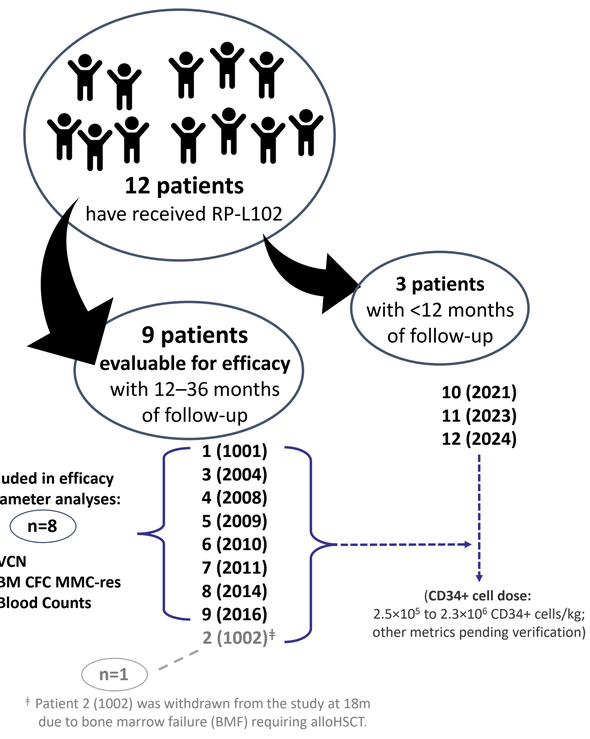
Patient Demographics and Investigational Product Metric for initial N=9 Patients

Subject #	Age at Enrollment (years)	Follow Up (months)	CD34+ Cells/kg	CFCs/kg	Mean VCN: Liquid Culture	Mean VCN: CFCs	Transduction Efficiency (%)	CFC Survival MMC 10nM (%)
1 (1001)	5	36	$2.0\times10^{5*}$	$5.2\times10^{4*}$	2.08	0.62**	67	33
2 (1002)	6	18†	$3.7\times10^{5*}$	$5.0\times10^{4*}$	2.21	0.92**	72	47
3 (2004)	3	24	4.8×10^{5}	$1.3\times10^{5‡}$	1.70	0.73	100	63
4 (2008)	2	21	3.2×10^{6}	$5.5\times105^{‡}$	1.65	1.56	97	63
5 (2009)	3	18	1.9×10^{6}	$3.1\times10^{5‡}$	2.16	0.76	61	45
6 (2010)	3	21	$4.1\times10^{6*}$	n/a	0.62	n/a	n/a	n/a
7 (2011)	5	18	$2.8\times10^{6*}$	n/a	1.46	n/a	n/a	n/a
8 (2014)	6	15	$5.4\times10^{5*}$	$3.6\times10^{4*}$	3.68	pending	pending	31
9 (2016)	2	12	$3.0\times10^{5*}$	$2.5\times10^{4*}$	1.96	0.64	88	64

Abbreviations: m: months; CFCs: colony forming cells; VCN: vector copy number; n/a: not available

* Per NC200 automated count (results in ~50% lower count vs. manual count used in FANCOLEN-I)
** Mean CFC VCN was assessed from a cryopreserved drug product sample
† Subject withdrawn from the study at 18m post-RP-L102 infusion; received successful alloHSCT
‡ Revised value following data validation

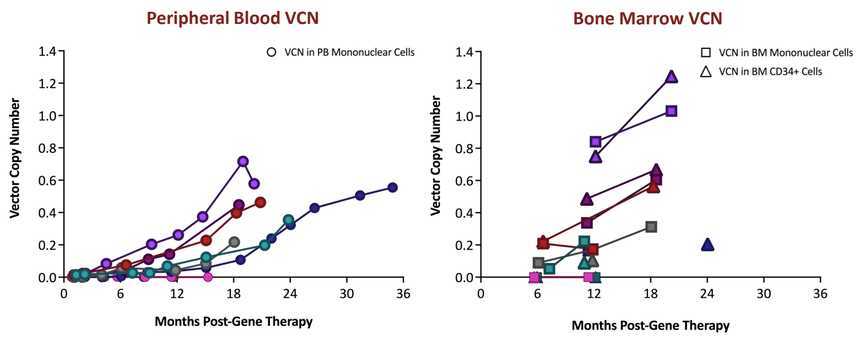
Data cut-off: April 4, 2022; Preliminary interim results are presented from ongoing clinical studies



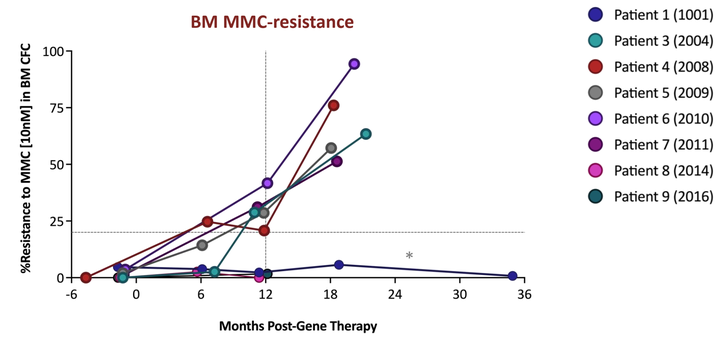
‡ Patient 2 (1002) was withdrawn from the study at 18m due to bone marrow failure (BMF) requiring alloHSCT.

Interim Efficacy Results

Progressive increases in gene markings in PB and BM sustained in 6 of 9 patients ≥1 year post-RP-L102



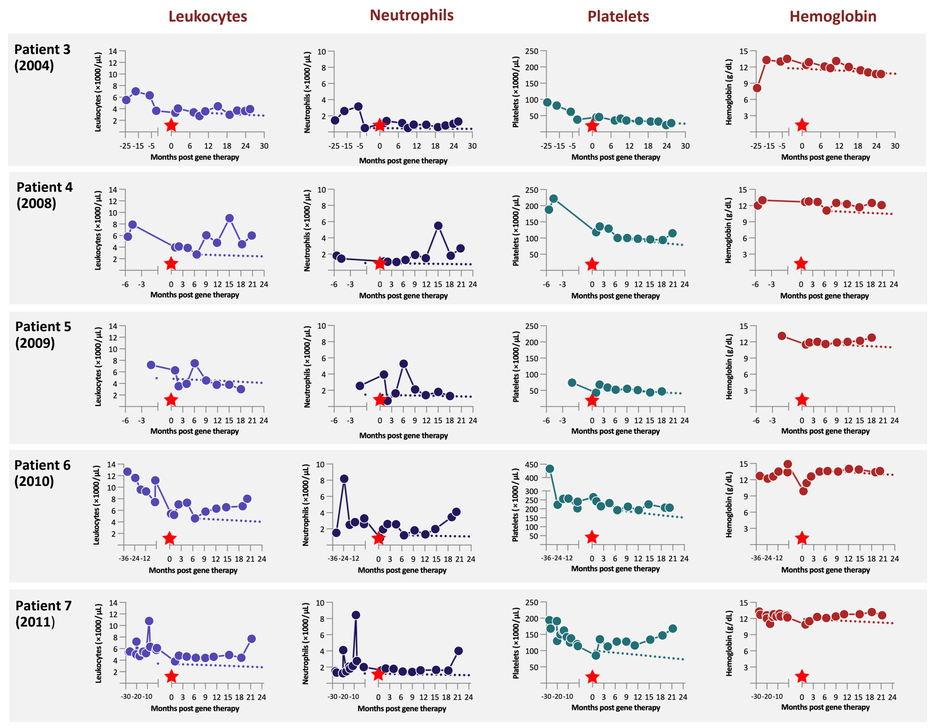
For 5 patients, increasing phenotypic correction by MMC resistance in BM CFCs ranging from 51% to 94% observed at 18–24 months post-RP-L102



* BM MMC-resistance for Patient 1 (1001)'s 24m assessment was not performed at study's central laboratories and is not included.
Not shown: BM MMC-res in Patient 2 (1002), who was withdrawn from the study at 18 months post-RP-L102 infusion

Genetic Correction Correlates with Phenotypic Improvement

Increased MMC-Resistance in BM CFCs associated with hematologic stabilization at ≥1 year post RP-L102 administration

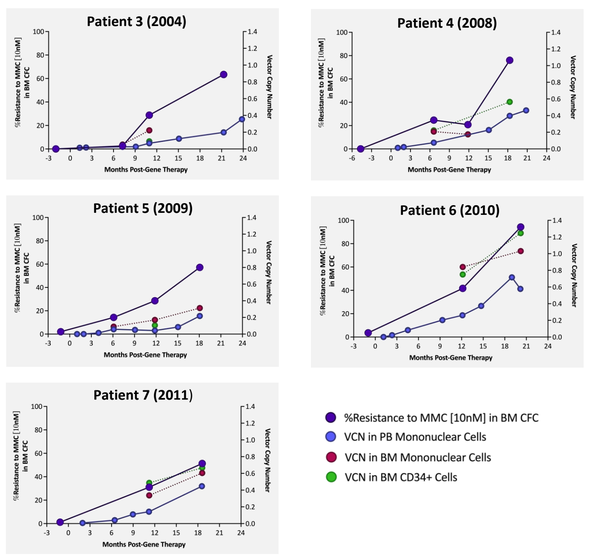


Dotted lines indicate projected blood count decreases based on natural history evaluation from n=139 age-matched FA-A patients (IFAR registry)

Concomitant blood count stabilization over 12–24 months in 5 of 5 patients with sustained and increasing MMC-resistance in BM CFCs

PB VCN strongly correlates with BM CFC MMC-Res at 12 months post-RP-L102 administration (r=0.83)†,*

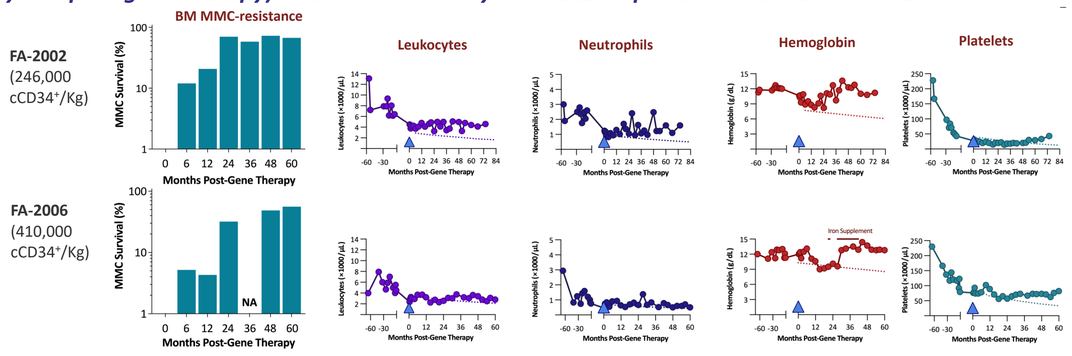
BM mononuclear cell VCN strongly correlates with BM CFC MMC-Resistance at 12 months post-RP-L102 (r=0.81)**



* r correlation calculated using data from n=7 patients (PB VCN data from Patients 2 [1002] and 4 [2008] not available);
** r correlation calculated using data from n=9 patients
† Patient 1 (1001) has to-date demonstrated more limited correlation between VCN and MMC-Resistance
- Genetic correction has been evident via VCN in PB (0.55 at 36m study visit) and in BM CD34+ cells (0.21 at 24m study visit).
- BM MMC-Resistance Δ was ~11% at 24m study visit (not performed at central lab), but BM MMC-Resistance was 0.8% at 36m study visit (central study lab).
- Patient required RBC transfusion at ~35 m post-RP-L102 in setting of potential intercurrent viral illness and recent vaccination.

FANCOLEN-I (Investigator-Initiated) Long-term Follow-up

≥20% BM CFC MMC resistance is associated with long-term hematologic stability (up to 6 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 months 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 age-matched FA-A patients (IFAR registry)
Source data verification has not yet been performed on most recent visits. Data cut-off April 26, 2022.

Conclusions

RP-L102 is a potentially definitive therapy to prevent FA-related BMF which, in contrast to allo-HSCT, can be administered without a suitable donor or conditioning related toxicities.

Comprehensive efficacy in multiple patients with ≥1 year of follow-up (evaluable patients)

- **5 of 9 patients have sustained, increasing BM CFC MMC resistance ranging from 51 to 94% at 18–24 months, and ≥20% at two consecutive timepoints ***
- **Increasing BM CFC MMC resistance is accompanied by concomitant genetic markings and hematologic stabilization**
- 6 patients with sustained peripheral blood and BM genetic correction (VCN)
- 1 patient had progressive BMF & underwent successful allogeneic transplant
- Potential for engraftment over 12–24 months follow-up will be evaluated in 2 patients for whom no/limited engraftment was identified at 12 months post RP-L102

Safety profile of RP-L102 is favorable

- Engraftment and phenotypic correction achieved in the ***absence of conditioning***
- 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
- RP-L102 related SAEs: 1 patient experienced an infusion-related reaction (transient, Grade 2)

**** Efficacy in ≥5 patients (observed over >1 year post-gene therapy) required to reject null hypothesis***

Disclosures: 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; Amgen: Consultancy/Advisor, Honoraria; Novartis: Consultancy/Advisor, Honoraria; Miltenyi: Consultancy/Advisor, Honoraria; SOBI: Consultancy/Advisor, Honoraria; Rocket Pharmaceuticals, Inc.: Consultancy/Advisor, Honoraria. Czechowicz: Beam Therapeutics: Consultancy, Equity Ownership; Decibel Therapeutics: Equity Ownership; Editas Medicine: Equity Ownership; Forty Seven Inc: Divested Equity in Last 24 Months; Gilead Sciences: Intellectual Property Rights; Global Blood Therapeutics: Equity Ownership; GV: Consultancy, Equity Ownership; Jasper Therapeutics: Intellectual Property Rights; Magenta Therapeutics: Equity Ownership, Intellectual Property Rights; Rocket Pharmaceuticals, Inc.: Research Funding; Spotlight Therapeutics: Consultancy, Equity; Stemodontics: Consultancy, Equity Ownership. Booth: SOBI: Consultancy, Honoraria; Orchard Therapeutics: Consultancy, Honoraria; Takeda: Honoraria; Rocket Pharmaceuticals, Inc.: Consultancy; GSK: Honoraria. Agarwal: There are no relationships to disclose. Zubicaray: Novartis: Consultancy. Río: Rocket Pharmaceuticals, Inc.: Equity Ownership, Patents & Royalties, Research Funding. Navarro: Rocket Pharmaceuticals, Inc: Patents & Royalties, Research Funding, Equity Ownership. Chetty: There are no relationships to disclose. O'Toole: There are no relationships to disclose. Xu-Bayford: There are no relationships to disclose. Ancliff: There are no relationships to disclose. Sebastián: There are no relationships to disclose. Choi: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. Zeini: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. Nicoletti: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. Wagner: Rocket Pharmaceuticals, Inc: Consultancy, Equity Ownership; ASC Therapeutics: Consultancy; Bluebird Bio: Consultancy; Vertex Pharmaceuticals: Consultancy; Magenta Therapeutics: Consultancy. Rao: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. Thrasher: Orchard Therapeutics: Consultancy and Equity Ownership; Rocket Pharmaceuticals, Inc.: Consultancy; 4Bio Capital: Consultancy; Generation Bio: Consultancy and Equity Ownership. Schwartz: Rocket Pharmaceuticals, Inc.: Employment, Equity Ownership. Roncarolo: There are no relationships to disclose. Bueren: Rocket Pharmaceuticals, Inc.: Consultancy; Other: 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 and receives funding for research.

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