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

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Abstract # 4775

Introduction

Fanconi anemia (FA) is a rare inherited DNA repair disorder characterized by:

- Progressive bone marrow failure (BMF); 80% of patients experience BMF within first decade of life
- 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.

Allo-HSCT is curative of BMF, but associated with significant short- and long-term toxicities, especially for ~80% pts who do not have an HLA-identical sibling donor

- 100-day transplant-associated mortality
- Graft-versus-host disease (GVHD)
- 3–4x increased risk for solid organ malignancies over high FA-associated cancer risk; ↑↑ with GvHD
- HSCT-associated coronary artery disease, musculoskeletal & neurocognitive dysfunction, endocrinopathies, infertility

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 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 the FANCOLEN-I trial



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

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:

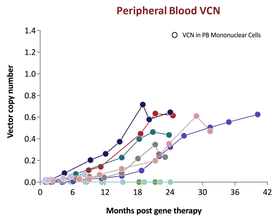
- FA complementation group A
- Minimum age: 1y
- Maximum age: US Ph 1 (12y); US Ph 2 (none); EU Ph 2 (17y)
- BM CD34+ cell concentration ≥30 CD34+ cells/µL (from aspirate)
- US Ph 1 only : At least 1 hematologic parameter (Hb, ANC, or Plt) below lower limit of normal

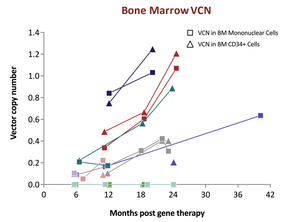
Exclusion criteria:

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

Interim Efficacy Results

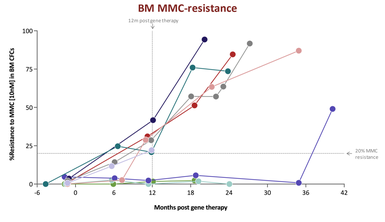
Progressively Increasing and Sustained Genetic Correction in 7 of 10 patients ≥1 year post-RP-L102





Not shown: PB and BM VCN in Patient 2 (1002), who was withdrawn from the study at 18 months post-RP-L102 infusion
BM VCN not available at some stipulated time points due to insufficient sample to run assay

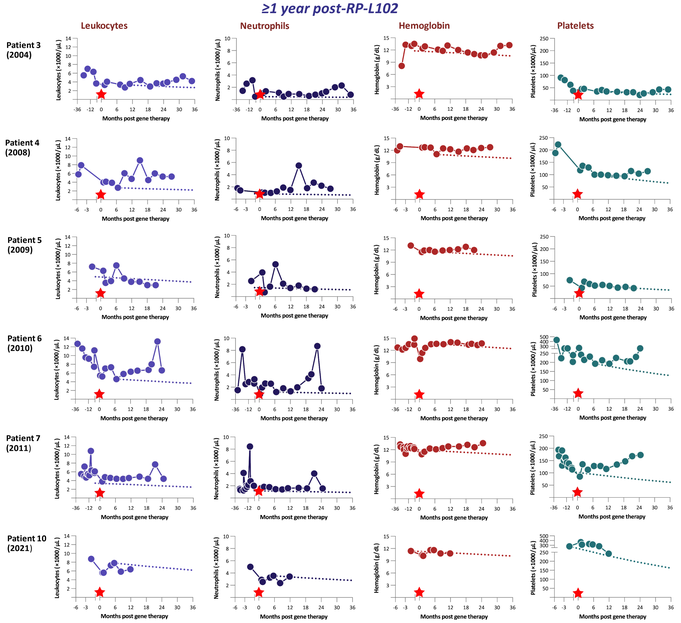
*Sustained BM CFC MMC Resistance observed in at least 6 patients over 1-3 years post-RP-L102**



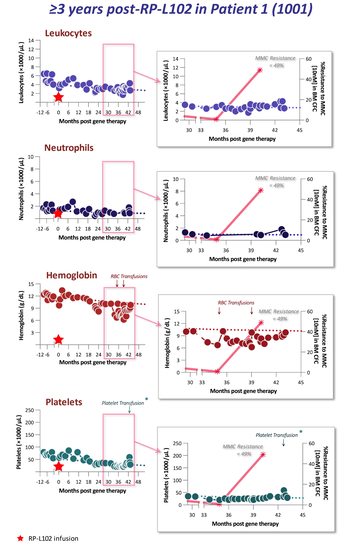
Not shown: MMC Resistance in Patient 2 (1002), who was withdrawn from the study at 18 months post-RP-L102 infusion
* One additional patient (Patient 1: 1001) was noted to have BM MMC resistance of 49% at ~40 months post-RP-L102 infusion

Phenotypic Improvement and Hematologic Stabilization

Increased MMC-Resistance in BM CFCs associated with Hematologic Stabilization at ≥1 year post-RP-L102



Increased BM CFC MMC Resistance Evident at ≥3 years post-RP-L102 in Patient 1 (1001)



Patient 1 (1001) developed BM MMC resistance of 49% at 40 months post-RP-L102 infusion and has had recent relative blood count stabilization and potentially decreasing transfusion requirements.

* Recent platelet transfusion was administered as prophylaxis in context of traumatic nasal fracture and cerebellar contusion.

Concomitant blood count stabilization over 12–36 months in 6/6 patients with BM MMC ≥20%

Hematology up to the most recent scheduled visit prior to lymphoma diagnosis/therapy is shown for Patient 5 (2009). Dotted lines indicate projected blood count decreases based on natural history evaluation from n=139 age-matched FA-A patients (IFAR registry, data on file)

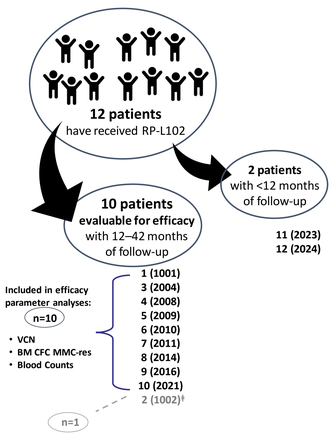
Patient Demographics and Investigational Product Metrics

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	42	$2.0\times10^{5*}$	$5.2\times10^{4*}$	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	36	4.8×10^{5}	1.3×10^{5}	1.70	0.73	100	63
4 (2008)	2	28	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	24	$4.1\times10^{6*}$	n/a	0.62	n/a	n/a	n/a
7 (2011)	5	24	$2.8\times10^{6*}$	n/a	1.46	n/a	n/a	n/a
8 (2014)	6	24	$5.4\times10^{5*}$	$3.6\times10^{4*}$	3.68	1.93	87	31
9 (2016)	2	21	$3.0\times10^{5*}$	$2.5\times10^{4*}$	1.96	0.64	88	64
10 (2021)	2	12	$2.3\times10^{6*}$	$4.3\times10^{5*}$	1.55	1.97	78	38
11 (2023)	5	9	$2.7\times10^{5*}$	$2.8\times10^{4*}$	1.70	2.16	87	50
12 (2024)	1	6	$1.8\times10^{6*}$	$1.7\times10^{5*}$	1.69	1.91	88	93

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 allo-HSCT

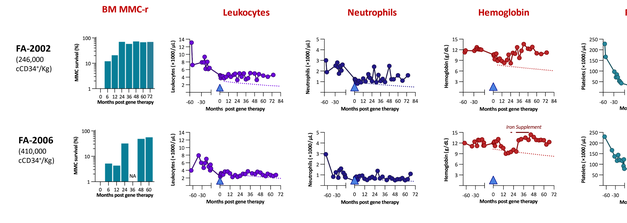
Data cut-off: October 26, 2022; Preliminary interim results are presented from ongoing clinical studies



† Patient 2 (1002) was withdrawn from the study at 18m due to bone marrow failure (BMF) requiring allo-HSCT.

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**

▲: RP-L102 infusion

Dotted lines indicate projected blood count decreases based on natural history evaluation from n=139 age-matched FA-A patients (IFAR registry, data on file)
Source data verification has not yet been performed on most recent visits. Data cut-off: September 21, 2022

Conclusions

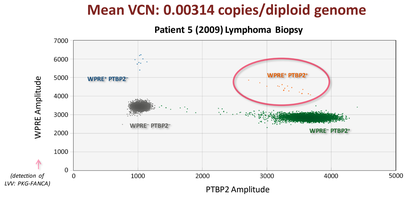
RP-L102 is a potentially curative therapy to prevent FA-related BMF which, in contrast to allo-HSCT, can be administered without a suitable donor or conditioning related toxicities.

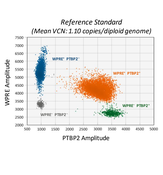
- **RP-L102 conferred phenotypic correction as demonstrated by sustained increased BM CFC MMC resistance, concomitant genetic correction and hematologic stabilization in at least 6 patients with ≥ 1 year of follow-up** (6 of 10 evaluable patients)
 - 1 additional patient with increasing PB and BM VCN, recent development of BM CFC MMC resistance and relative hematologic stability
- **Sustained engraftment, phenotypic correction, and hematologic stability achieved in the *absence of conditioning***
- **RP-L102 infusion is well tolerated with a highly favorable safety profile**
 - 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***

RP-L102 Safety Profile Appears Highly Favorable

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
- Induction chemotherapy for T-ALL was tolerated well with clinical complete response
- Negligible VCN in lymphoma was likely result of blood cells within tumor specimen

- Patients are treated without antecedent conditioning and attendant risks
- No signs of bone marrow dysplasia, clonal dominance or insertional mutagenesis to date 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**.

Disclosures: Czechowicz: 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, STIM Bio. 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. Booth: SOBI: Consultancy, Honoraria; Orchard Therapeutics: Consultancy, Honoraria; Takeda: Honoraria; Rocket Pharmaceuticals, Inc.: Consultancy; GSK: Honoraria. Agarwal: There are no relationships to disclose. Zubicaray: There are no relationships to disclose. 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. Eide: There are no relationships to disclose. Wagner: Rocket Pharmaceuticals, Inc: Consultancy, Equity Ownership; AGC 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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