Gene Therapy for Fanconi Anemia, Complementation Group A: Updated Results from Ongoing Global Clinical Studies of RP-L102

Agnieszka Czechowicz MD, PhD
Center for Definitive and Curative Medicine
Department of Pediatrics, Division of Stem Cell Transplantation and Regenerative Medicine, Stanford University School of Medicine
Lucile Packard Children's Hospital Stanford

Co Authors: Rajni Agarwal MD; Julián Sevilla MD, PhD; Paula Río PhD; Susana Navarro PhD; Brian C Beard PhD; Kenneth M Law PhD; Grace Choi BS; Eileen Nicoletti MD; John E Wagner MD; Claire Booth MBBS, PhD, MSc; Jonathan D Schwartz MD; Juan A Bueren PhD* and Maria Grazia Roncarolo MD*

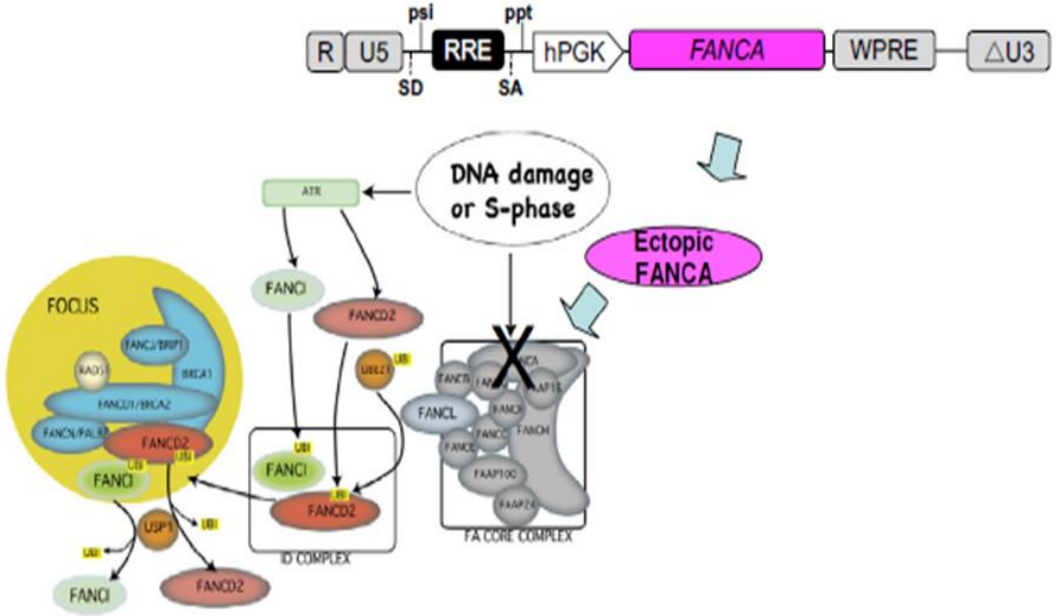
*Both authors contributed equally to this work.

Introduction

- Fanconi anemia (FA) is a rare genetic DNA repair disorder characterized by:
  - Progressive bone marrow failure (BMF), with 80% developing BMF within 1st decade of life
  - Predisposition to hematologic malignancies and solid tumors
  - Varied congenital abnormalities
- FA complementation group A (FA-A) accounts for 60-70% of FA
- Allogeneic hematopoietic stem cell transplant (HSCT) is frequently curative of FA-associated BMF, but its utilization and efficacy is limited by:
  - Donor availability
  - Graft-versus-host disease (GvHD)
  - Acute and long-term toxicities including increased risk of subsequent solid tumors

Gene Therapy for FA-A

Ex-vivo lentiviral (LV) mediated gene therapy for FA-A involves insertion of a functional *FANCA* gene into autologous FA-A CD34+ cells to confer resistance to DNA-damage & proliferative advantage to modified cells



- FANCOLEN-I,[1] a Phase 1/2 study, demonstrated evidence of engraftment, phenotypic correction, and stabilization of blood counts in FA-A patients
- Studies currently ongoing to evaluate efficacy and safety of RP-L102 in FA-A

RP-L102 Studies	N Planned	N Treated
US Ph 1	2	2
US Ph 2	5	3
EU Ph 2 (FANCOLEN-II)	5	4

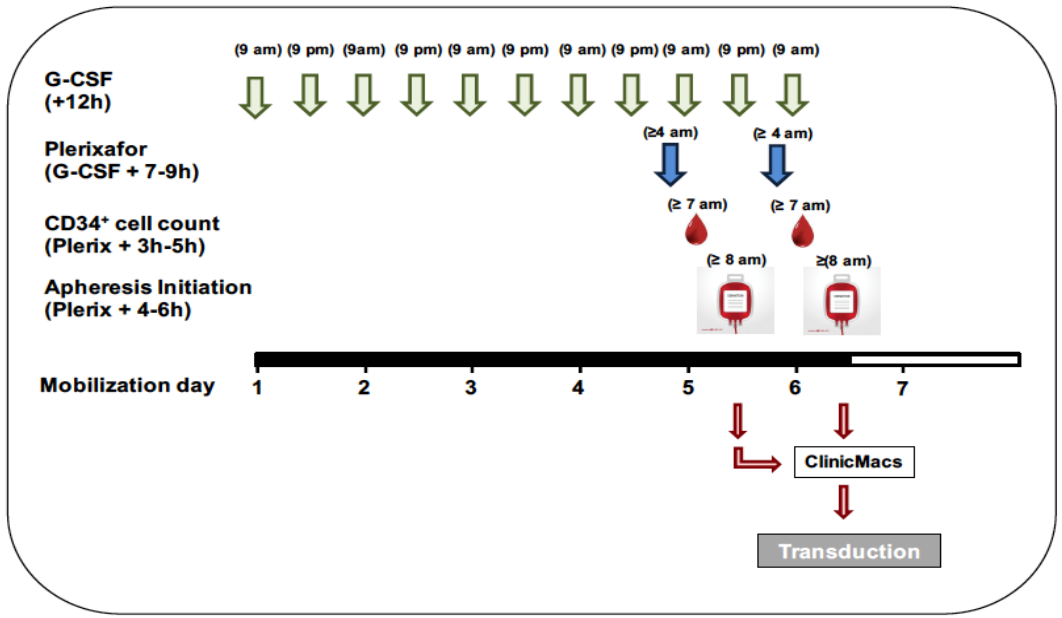
[1] Río P *et al*. Nat Med 2019; 25:1396-1401

RP-L102 Study Eligibility Criteria & Endpoints

RP-L102 Studies	US Phase 1, US Phase 2, and EU Phase 2 (FANCOLEN-II)	
Inclusion Criteria	FA complementation group A Minimum age: 1 *Maximum age: US Ph 1 (12 yrs); US Ph 2 (none); EU Ph 2 (17 yrs)* BM CD34+ concentration ≥ 30/µL (from aspirate); if BM CD34+ of 10-29/µL, then at least 2 of the following: Hb ≥ 11g/dL, ANC ≥ 900/µL, or Platelets ≥ 60,000/µL *US Ph 1 only : At least 1 hematologic parameter (Hb, ANC or Plt) below lower limit of normal*	
Exclusion Criteria	Available & eligible HLA-identical sibling donor MDS or leukemia (including associated cytogenetic abnormalities) Mosaicism with stable/improved blood counts	
Endpoints	**Efficacy**	**Engraftment**: Peripheral blood (PB) and 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 ***Efficacy in 5 of 12 subjects (observed over 1-3 years post rx) required to reject null hypothesis***
	Safety of RP-L102	

RP-L102 Study Design

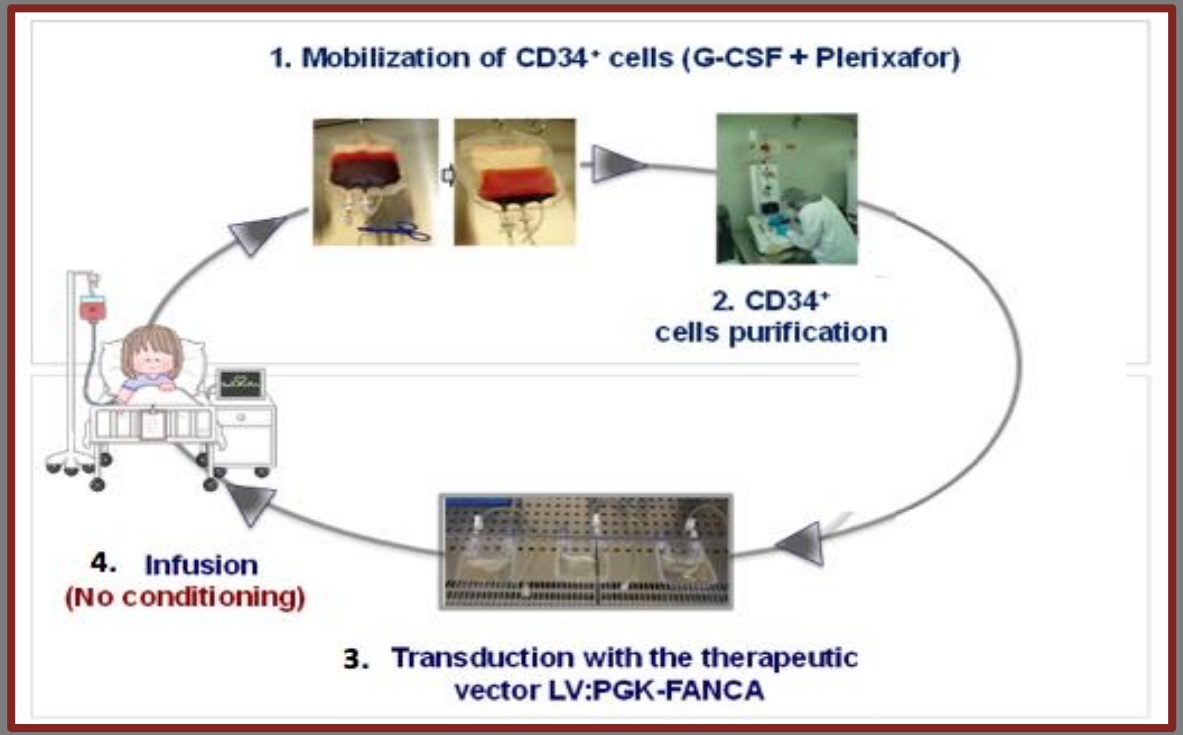
CD34+ cell mobilization protocol with G-CSF and plerixafor:



G-CSF and plerixafor administered over 6-days with apheresis conducted on 2 consecutive days.

PB counts of at least 5 CD34+ cells/µL are required to initiate apheresis.

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*.

RP-L102 Treated Study Subjects

Phase	Subject #	Site	Age at Enrollment	Gender	Follow-up
PHASE 1	1 (1001)	US	5	F	18M
	2 (1002)	US	6	F	18M
	3 (2004)	Spain	3	M	12M
PHASE 2	4	Spain	2	F	2M
	5	Spain	3	M	2M
	6	US	3	M	2M
	7	US	5	F	2M
	8	UK	6	F	1M
	9	US	2	M	-

- 9 subjects treated across 3 clinical sites, 2 under Phase 1 and 7 under global Phase 2
- All subjects ≤ 6 years at enrollment
- 3 subjects have ≥ 12 months of follow-up; remaining treated more recently with limited follow-up
- Note: Follow-up has been complicated by COVID-19 pandemic

RP-L102 Investigational Product Metrics

Phase	Subject #	CD34+ Cells/kg^	CFCs/kg^	Mean VCN: Liquid Culture	Mean VCN: CFCs	Transduction Efficiency (%)	CFC Survival MMC 10nM (%)
PHASE 1	1 (1001)	2.0×10^5	5.2×10^4	2.08	0.62	67	33
	2 (1002)	3.7×10^5	5.0×10^4	2.21	0.92*	72	47
PHASE 2	3 (2004)	4.8×10^5	1.1×10^5	1.70	0.73	100	63
	4	3.2×10^6	2.8×10^5	1.65	1.56	97	62
	5	1.9×10^6	1.5×10^5	2.16	0.76	61	45
	6	4.1×10^6	Pending	0.62	Pending	Pending	Pending
	7	2.8×10^6	Pending	1.46	Pending	Pending	Pending

Overall DP metrics are consistent with the more optimally treated subjects from FANCOLEN-I study

<u>Median values</u>:
VCN (liq) 1.7
VCN (CFC) 0.76
TD efficiency 72%
CFC MMC-res 47%

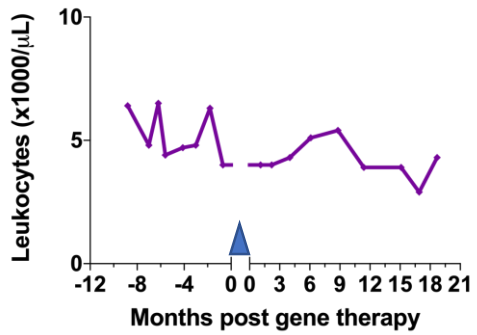
Overall transduction and MMC-resistance levels in DP are consistent with high degree of corrected HSPCs

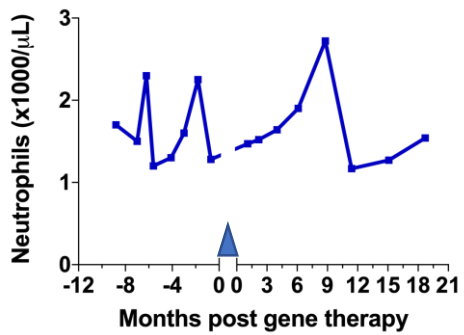
* Mean CFC VCN was assessed from a cryopreserved drug product sample.

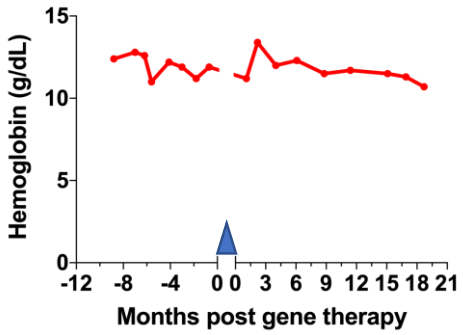
^ Per NC200 automated count (results in ~50% lower count vs. manual used in FANCOLEN-I).

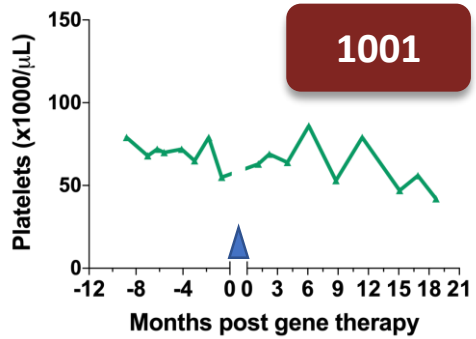
CFCs: colony formin cells
VCN: vector copy
MMC: mitomycin-C

RP-L102 Treated Study Subjects with >12 mo f/u



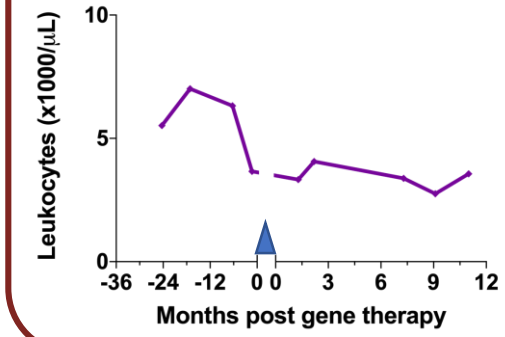


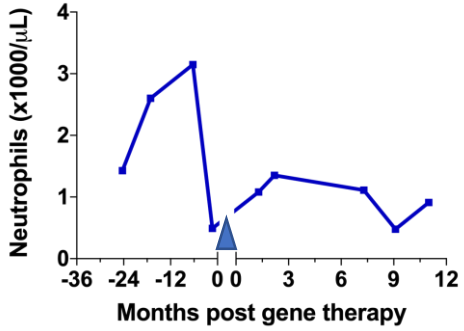


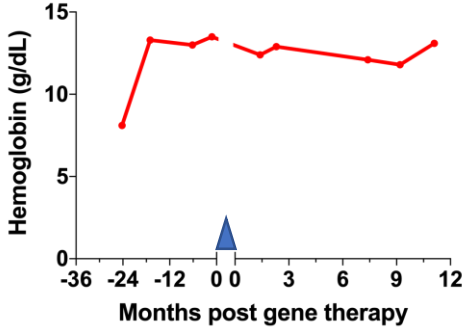


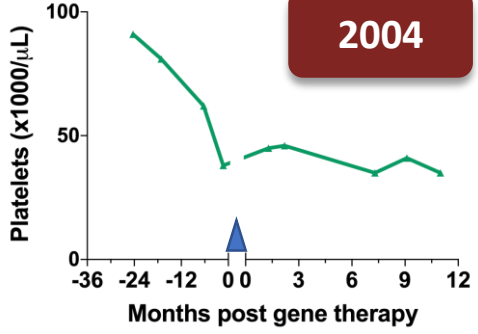
1001

- **Before to gene therapy, decreases in multiple blood lineages over prior 12-24 months**



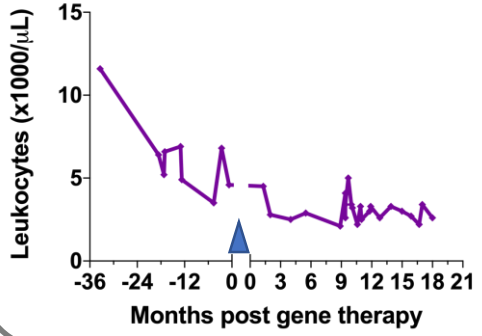


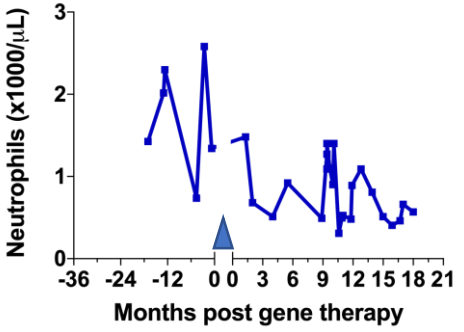


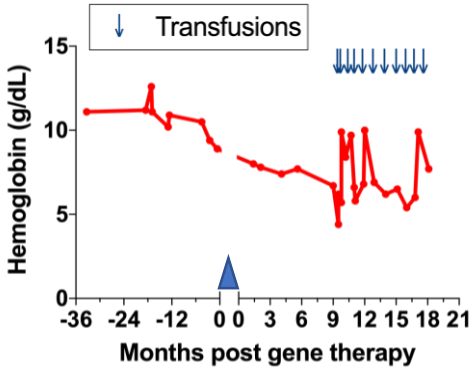


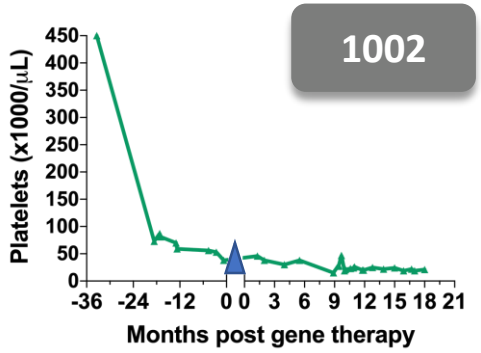
2004

- **Post gene therapy, stability across multiple blood lineages observed over 12-18 months**









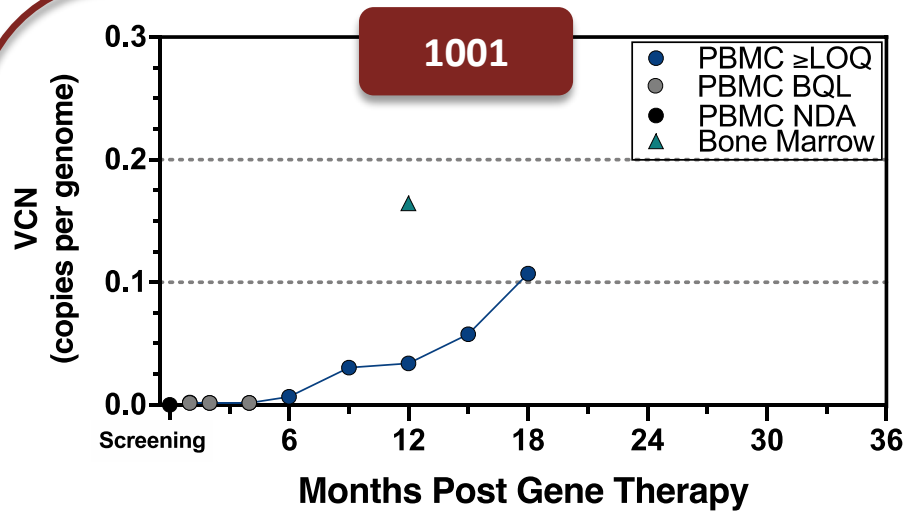
1002

- **One subject with *Influenza B infection* 9 months post-rx; Required transfusions and subsequent [illegible]T at 18 months post-rx**

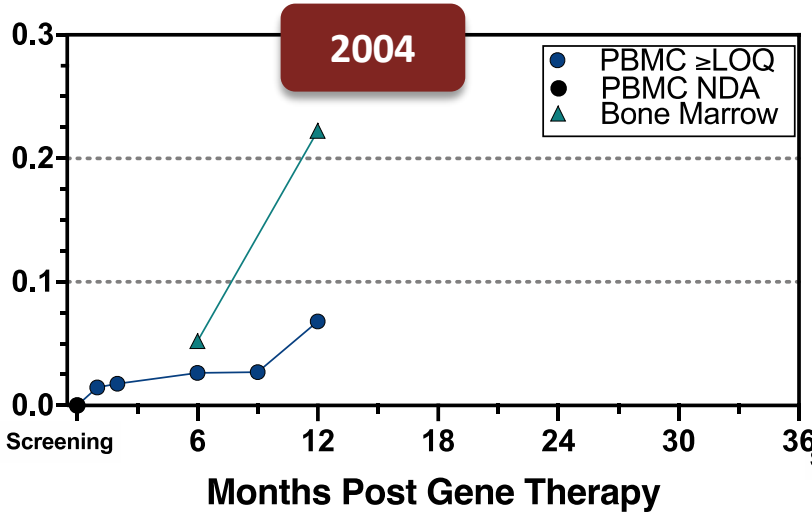
RP-L102 Treated Study Subjects with >12 mo f/u

N = 3 with ≥ 12M Months of Follow-up

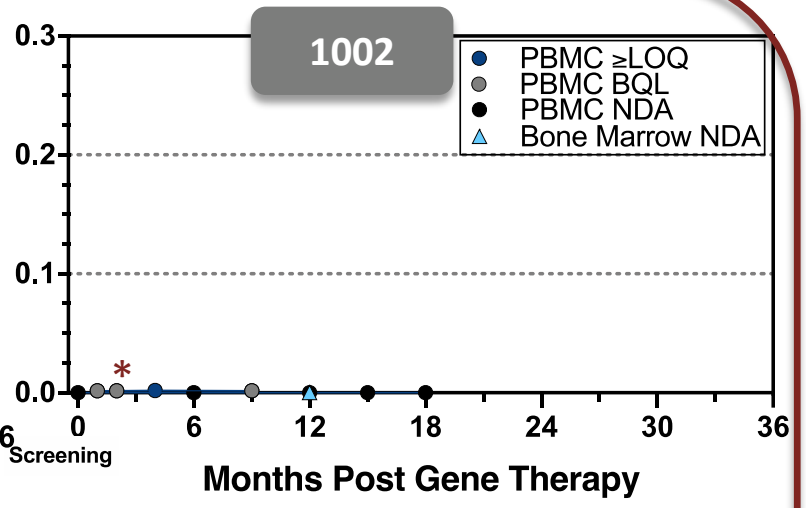
- 2 of 3 show increasing evidence of engraftment
- 1 subject's course (1002) complicated by *Influenza B* infection; required BMT



BM progenitors resistant to 10 nM MMC at 18 months increased from baseline; final result pending



BM progenitors resistant to 10 nM MMC at 12 months to levels comparable to BM VCN; final result pending



Presence of BM progenitors resistant to 10 nM MMC at 12 months suggests that engraftment occurred, but with insufficient rapidity to prevent influenza/FA-mediated BMF

LOQ = Limit of quantitation BQL= Below quantitation limits NDA = No detectable amplification

* Early time points had gene marking that was below quantification limits (BQL)

Summary of RP-L102 Treated Study Subjects

PB VCN available for N = 7

5 of 7 show preliminary evidence of engraftment

N = 3 with ≥ 12M VCN

- 2 of 3 show increasing evidence of engraftment
- 1 subject's course (1002) complicated by *Influenza B* infection; required BMT

N = 4 with early VCN (2M)

3 show early evidence of engraftment (0.01-0.02)

- All subjects clinically stable post treatment; the subject who required BMT underwent transplant and engrafted without complications
- RP-L102 related SAEs: 1 transient infusion-related reaction (Grade 2)
- Subject follow-up has been challenged by COVID-19 pandemic but enrollment and follow-up continue, with emphasis on minimized patient travel and optimal safety precautions

Conclusions

- 9 subjects treated to date with RP-L102 across Ph 1 and Ph 2 studies at 3 clinical centers
  - 7 subjects with follow-up data: 3 with ≥ 12M follow-up
- Safety profile of RP-L102 appears highly favorable
  - Subjects treated without conditioning
  - No signs of dysplasia or other concerning features
- Evidence of preliminary engraftment observed in 5 out of 7 subjects to-date*
- Evidence of increasing engraftment, MMC-resistance and stable blood counts in 2 out 3 subjects with ≥ 12M follow-up
  - 1 subject's course complicated by *Influenza B* resulting in progressive BMF

** Efficacy in 5 of 12 subjects (observed over 1-3 years post rx) required to reject null hypothesis*

Acknowledgements

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

Maria Grazia Roncarolo MD PhD
Rajni Agarwal MD
Elisabeth Merkel RN

Hospital Infantil Universitario Niño Jesús

Julián Sevilla MD PhD

UCL GREAT ORMOND STREET INSTITUTE OF CHILD HEALTH

Claire Booth MBBS PhD MSc
Philip Ancliff MA MRCP MRCPath
Adrian Thrasher MB PhD FMedSci

Ciemat

ciberer Centro de Investigación Biomédica en Red Enfermedades Raras

Hospital Universitario Fundación Jiménez Díaz Grupo quirónsalud

Juan Bueren PhD
Paula Río PhD
Susana Navarro PhD

John E. Wagner MD
Margaret MacMillan MD
Cindy Eide MS

rocket pharma

Eileen Nicoletti MD
Brian Beard PhD
Ken Law PhD
Grace Choi
Miriam Zeini Moreno PhD
Gayatri Rao MD JD
Jonathan Schwartz MD