Early Results from the MOMENTUM Trial, A Phase 1/2 Study of ARU-1801 Gene Therapy with Reduced Intensity Conditioning for Sickle Cell Disease (SCD)

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Disclosures

- No relevant conflicts of interest to disclose

Sickle Cell Disease (SCD), a devastating genetic disease caused by abnormal sickle hemoglobin

Sickle Cell Disease

- Leads to vaso-occlusive events (VOEs) and hemolysis
- Major complications include chronic hemolytic anemia, stroke, and progressive organ damage
- **Mean age of death in the US is 44 years**[1]

High unmet need for curative therapies

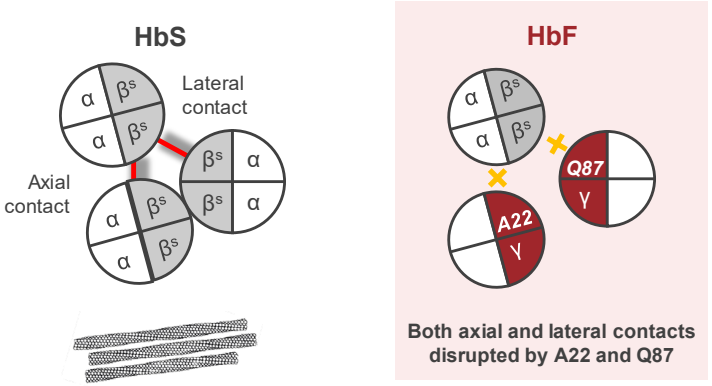
- Persistent VOEs with current medical therapy options
- Less than 20% of sickle cell patients have a matched sibling donor
- Complications associated with allogeneic transplant are not well tolerated in adults with SCD

1. Paulukonis S & Hagar R. Blood. 2017 Dec; 130(1); 2133

Fetal Hemoglobin (HbF) is the most potent anti-sickling globin and is the ideal choice for the treatment of SCD

Mechanistic benefits of HbF

- HbF disrupts both axial and lateral contacts in HbS polymers



- HbF has 1.5-2X higher affinity for oxygen than HbA and HbS[1]

Clinical benefits of HbF

- **HbF levels > 8.6%** improves survival [2]
- **HbF levels > 20%** reduce hospitalizations by 2-4-fold [3,4]
- **HbF levels > 30%** can result in **asymptomatic disease**[5]

Notes and Sources:
1. Pearson Education
2. Platt et al., 1984
3. Powars et al., 1984
4. Estepp et al., 2017
5. Ngo et al., 2011 demonstrated HbS/HPFH is asymptomatic and typically shows pan-cellular distribution of HbF >30%

ARU-1801 generates HbF^{G16D} and is able to engraft with reduced intensity conditioning

ARU-1801

- Self-inactivating lentiviral vector
- Modified γ-globin gene for a novel, highly potent variant of fetal hemoglobin (HbF): HbF^{G16D}
- *Ex vivo* transduction of autologous CD34+ cells

Unique features confer high potency

1	**More HbF per vector copy**	Unique G16D point mutation drives higher HbF levels per vector copy
2	**Higher potency HbF**	HbF^{G16D} has a more potent anti-sickling effect than endogenous HbF
3	**Preserved stemness**	Unique manufacturing process

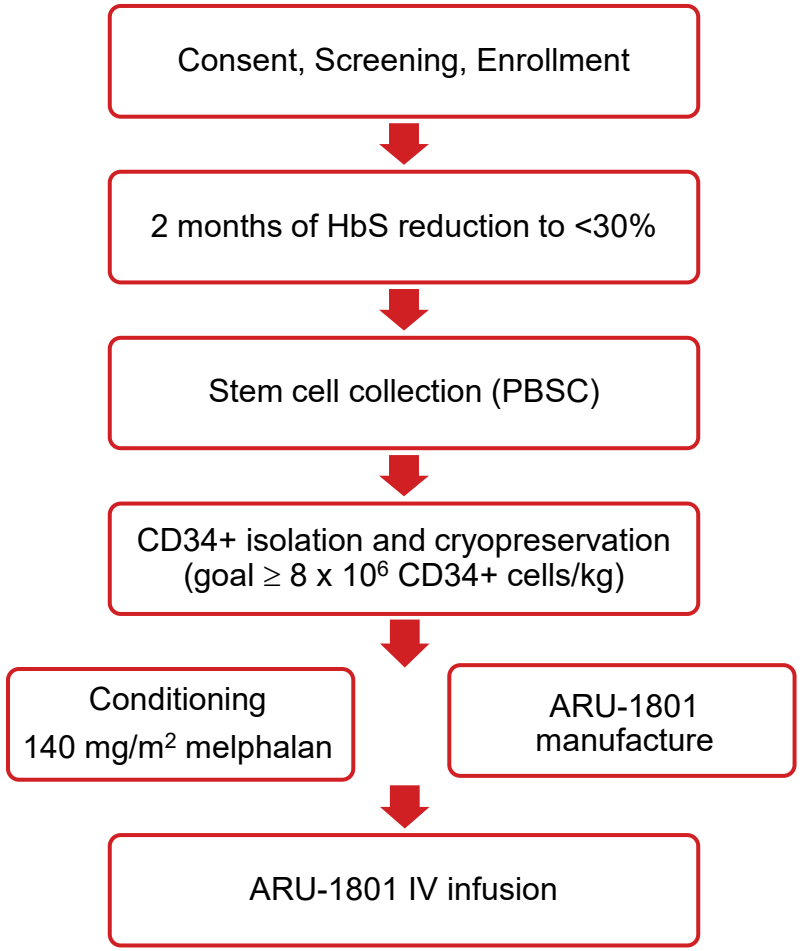
The MOMENTUM study is a Phase 1/2 trial of ARU-1801 utilizing Reduced Intensity Conditioning (RIC) in patients with severe SCD

Key Inclusion Criteria

- HbSS / HbS-b0 / HbS-b+ thalassemia)
- 18-45 years of age
- Patients with severe SCD (frequent painful VOEs, 2 or more lifetime ACS, or one ACS requiring ICU admission or requiring chronic transfusions)
- Failed hydroxyurea, actively refused to take it, or have no access
- No matched sibling donor or refused allogeneic transplant

Key Exclusion Criteria

- Hx of stroke or on disease modifying therapy for moderate to high risk for stroke
- Patients with alpha thalassemia (2 or more deletions)



Manufacturing process changes were implemented with the goal of improving efficacy

	Process I manufacturing	Process II manufacturing
	Patients 1 and 2	Patient 3
Collection method	**BMH and PBSC (w/Plerixafor)**	**PBSC (w/Plerixafor)**
Collection detail	**Standard BMH (20 ml BM/kg per harvest)** **Standard PBSC collection with plerixafor**	**Optimized PBSC collection** • **Shorter window from plerixafor to apheresis start** • **Deeper collection interface**
Vector	**Original conditions**	**Improved purity and transfection**
Transduction		**Optimized transduction conditions**

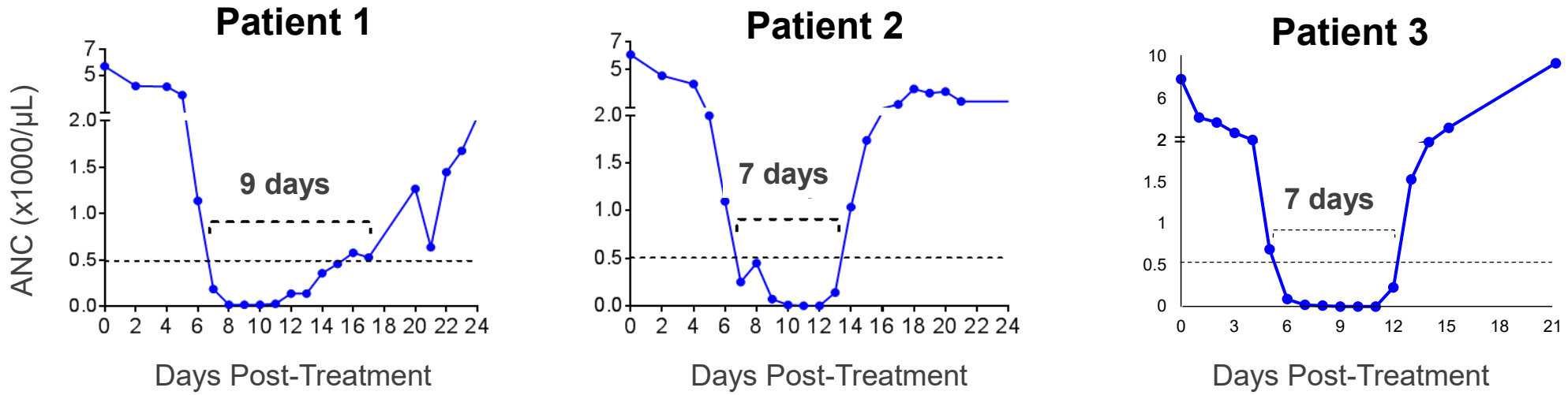
*Total HbF represents endogenous HbF plus HbFG16D derived from ARU-1801, and is presented as a proprostion of endogenously product Hbs (excluding HbA from transfused blood).
BMH – bone marrow harvest, PBMC = peripheral blood mononuclear cell, DP = drug product,

Characteristics of the first 3 subjects dosed with ARU-1801

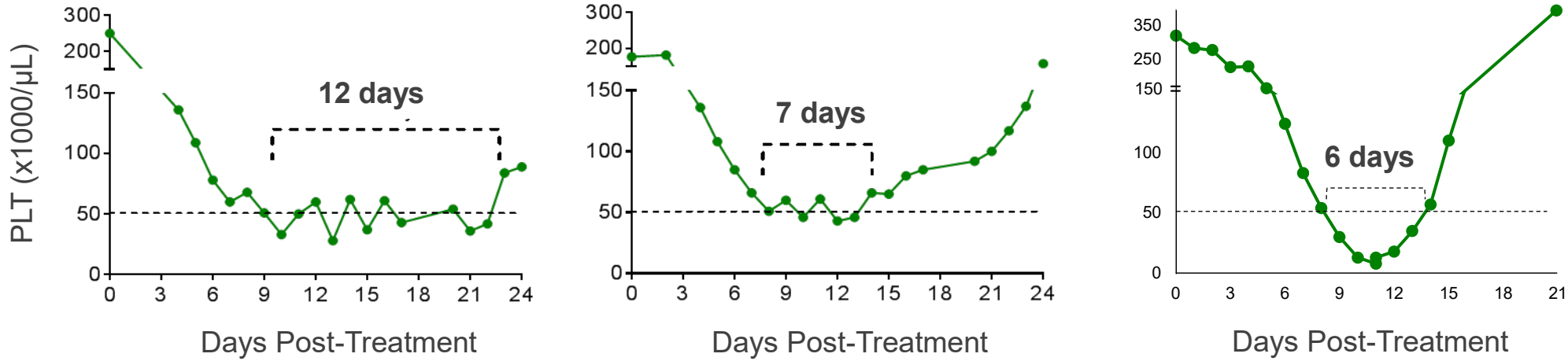
	Patient 1	Patient 2	Patient 3
Baseline demographics	34-year old female	24-year-old male	19-year-old female
Genotype	$HbS\beta^0$	$HbS\beta^+$	HbSS
Prior Disease-Modifying Therapies	Hydroxyurea Supportive care with analgesics	Hydroxyurea Supportive care with analgesics	Chronic blood transfusions Hydroxyurea
Disease-Modifying Therapies at Consent	Supportive care only	Hydroxyurea	Chronic blood transfusions
Pertinent Medical History	Repeat ACS, leg ulcers, Heterozygosity for G6PD deficiency	ACS, bacterial sepsis	ACS, pulmonary embolism, transfusional hemosiderosis
Latest follow-up	**36 months**	**30 months**	**9 months**

Cytopenia duration is consistent with RIC

Neutropenia



Thrombocytopenia

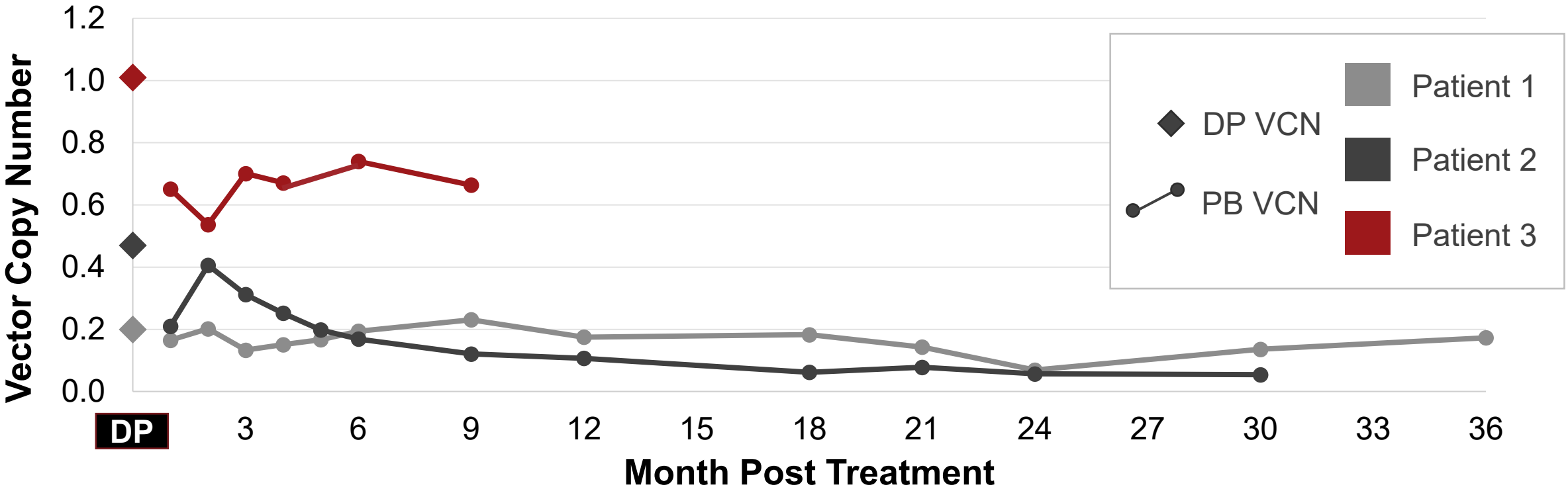


1. ASGCT 2019 Oral Abstract Session 123, Abstract 50, Monday 29 April 2019 by Dr. Punam Malik
2. Aruvant data

No Serious Adverse Events

	Patient 1	Patient 2	Patient 3
ARU-1801 related			
Infusion AEs	**None**	**None**	**None**
Late AEs	**None to date (at 36 months)**	**None to date (at 30 months)**	**None to date (at 9 months)**
Vector insertion	**Polyclonal engraftment with no evidence of clonal expansion**		
Chemotherapy related			
Serious	**None**	**None**	**None**
Non-serious	**Cytopenias, mucositis, nausea, vomiting, cellulitis, elevated RFT and LFTs, alopecia**	**Cytopenias, mucositis, c-line infection, elevated LFTs**	**Cytopenias, mucositis, nausea, vomiting, febrile neutropenia, alopecia**

Durable engraftment seen to 36 months, with strongest engraftment to date from Process II (Patient 3)



Infused CD34+ cell dose: **Patient 1: 1.4 e6/kg** **Patient 2: 7.1 e6/kg** **Patient 3: 6.8 e6/kg**

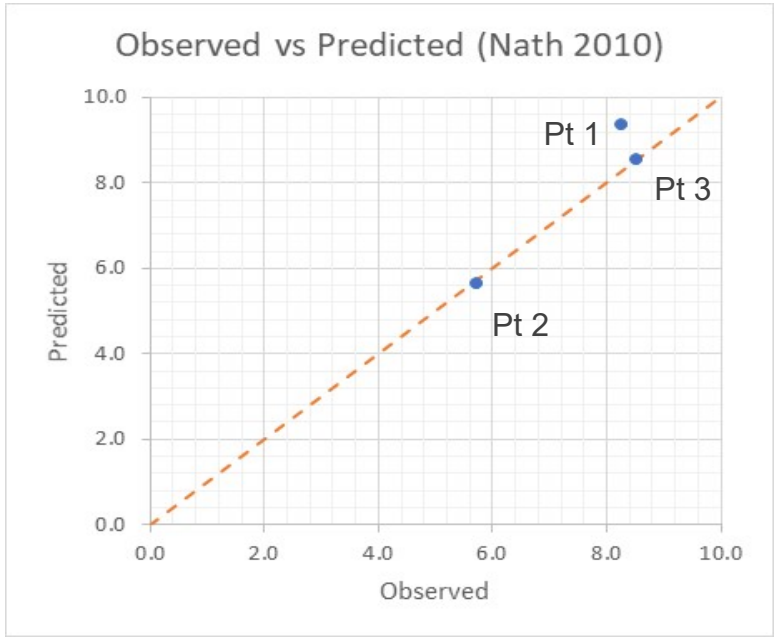
DP: Drug Product (ARU-1801) PB: Peripheral Blood

Renal based melphalan dosing may be needed in patients with hyperfiltration

	Patient 1	2	3
eGFR[1] (normal 90-120)	78	200	108
Melphalan Plasma AUC[2]	8.27	5.73	8.52

- Melphalan is renally excreted
- Target range melphalan AUC: 6.6 – 9.2 mcg.h/mL

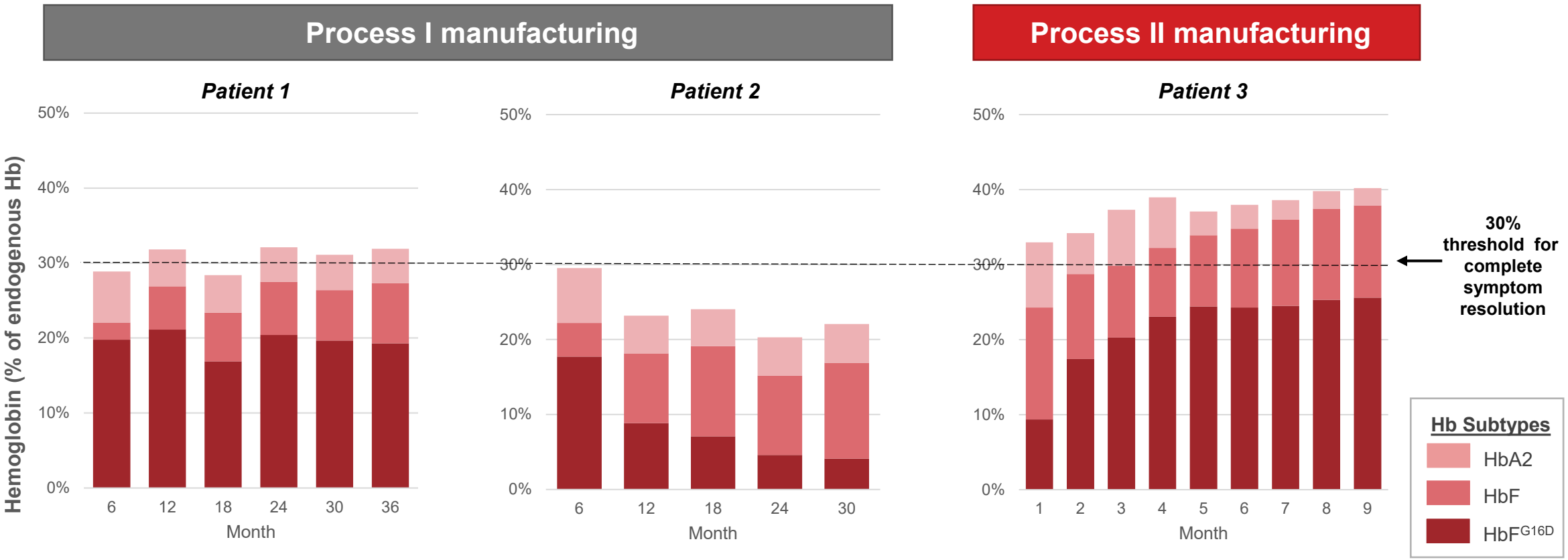
Published model[3] accurately predicted AUC in our 3 subjects



Potential to move to guided melphalan doses for patients with renal hyperfiltration

1. eGFR in units of mL/min
2. Melphalan plasma AUC in units of mcg.h/mL
3. Nath, CE et alt, British J Clin Pharm 2010 May; 69(5): 484–497

ARU-1801 has demonstrated durable engraftment through 36 months and potentially curative HbF levels



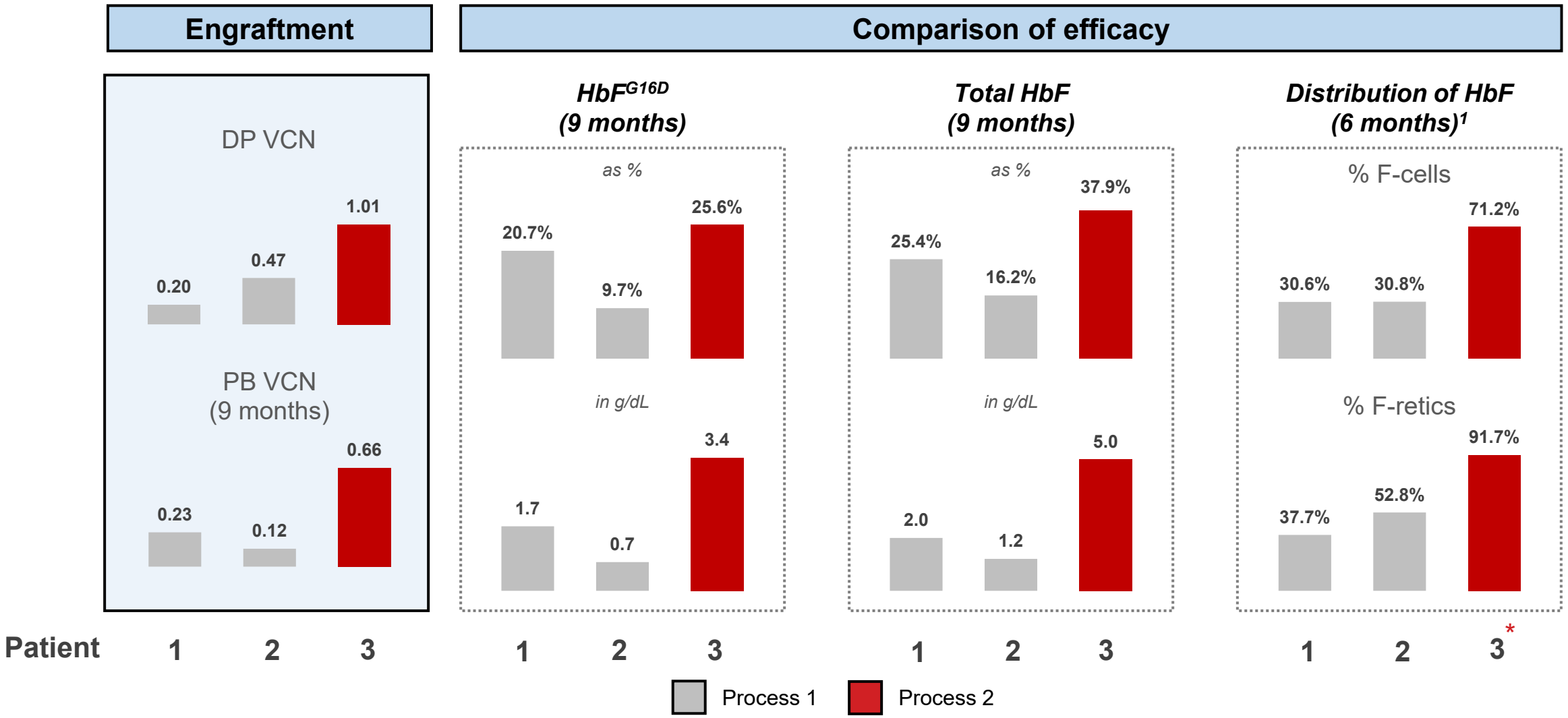
Durable engraftment through 36 months

Durable antisickling Hb levels through 30 months

38% total HbF expression at 9 mo

1. ASGCT 2019 Oral Abstract Session 123, Abstract 50, Monday 29 April 2019 by Dr. Punam Malik
2. Aruvant data
3. % of endogenous Hb expressed as % of sum (HbF^{G16D}, HbF, HbA2, and HbS) to account for transfused HbA blood. Patient 2 expresses ~3% endogenous HbA which is not included in the endogenous Hb calculation as it cannot be distinguished from exogenous HbA during transfusions

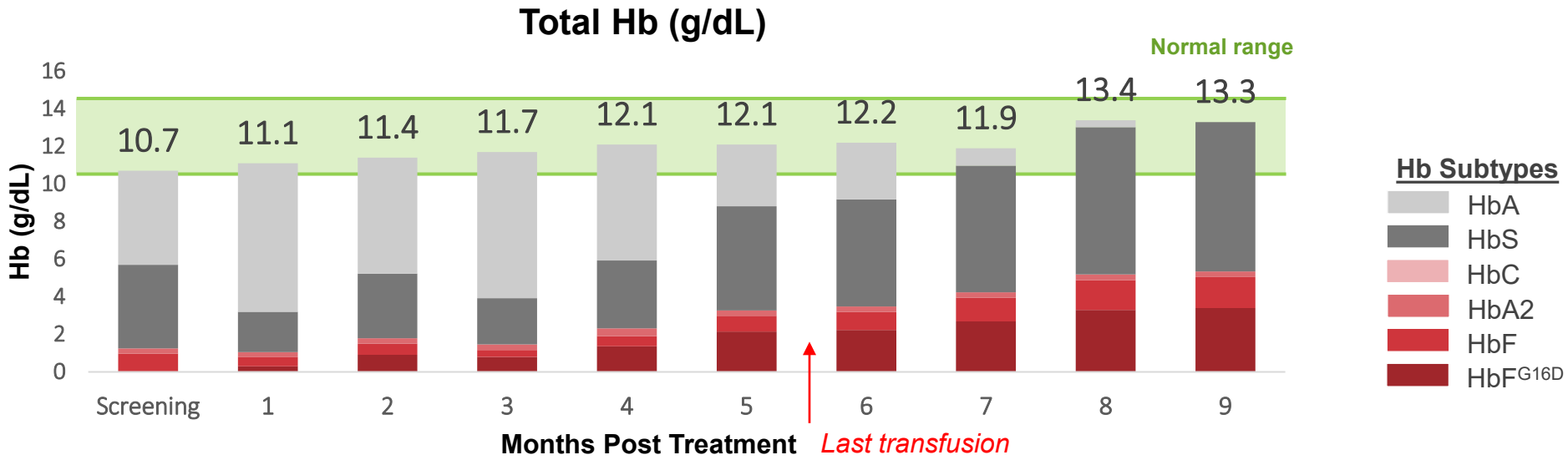
Process II results in significantly improved drug product profile, with improvements in all metrics of efficacy

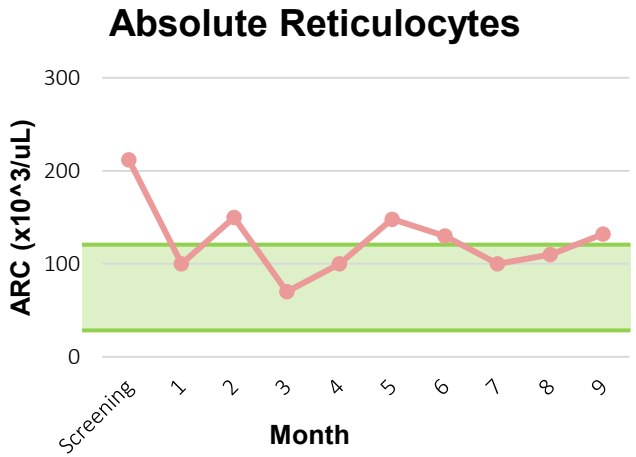


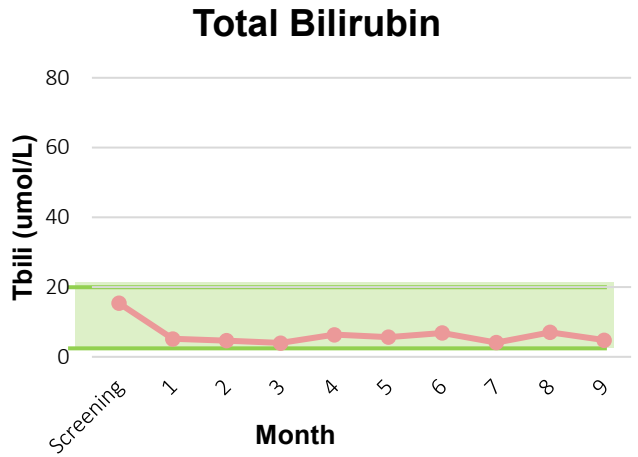
* Expected to rise as transfused blood declines. 6 month value reflects 25% HbA from transfused blood.

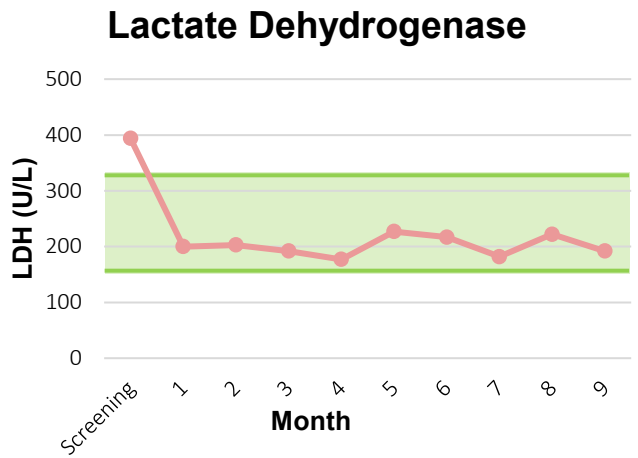
1. Hb electrophoresis monitored monthly in Year 1. F-cells and F-retics are collected at 6months and 12 months post-infusion

Patient 3 has normalized total Hb and measures of hemolysis









Note: Labs at Screening are used as “Baseline’

All patients have realized clinically meaningful reductions in VOEs

		Hospitalized VOEs			Total VOEs		
	Patient	Pre-treatment (24 mo)	Post-treatment (24 mo)	***Reduction (%)***	Pre-treatment (24 mo)	Post-treatment (24 mo)	***Reduction (%)***
Process I	1	7	**1**	***86%***	41	**3**	***93%***
Process I	2	1	**0**	***100%***	20	**3**	***85%***
Process II	3	6	**0 at 9 mo**	***100%***	12	**0 at 9 mo**	***100%***

ARU-1801 has demonstrated meaningful clinical benefit for patients with severe SCD using reduced intensity conditioning

- ARU-1801 is an investigational lentiviral gene therapy delivering a modified gamma-globin gene that encodes novel HbF^{G16D}
- ARU-1801 was found to be safe with no ARU-1801 or chemotherapy related serious adverse events reported
- Long term engraftment of up to 36-months was feasible with ARU-1801 without the use of myeloablative chemotherapy
- Clinically meaningful long-term reductions in disease burden was observed with ARU-1801, as seen with significant reductions in hospitalized VOEs and total VOEs
- Process improvements correlated with improved efficacy
  - >37% total HbF and highest HbF^{G16D} to date and still rising
  - Near pancellular Hb F distribution in reticulocytes
  - No VOEs through 9 months post treatment

ARU-1801 has demonstrated that a gene therapy for SCD with reduced intensity conditioning is possible, and an important future option for patients

Acknowledgements

- Patients who have enrolled into this trial, their families and caregivers
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For more information about this study, visit:

www.momentumtrials.com

or

ClinicalTrials.gov (NCT02186418)