American Society of Hematology
Helping hematologists conquer blood diseases worldwide

Safety and Efficacy of ARU-1801 in Patients with Sickle Cell Disease: Early Results from the Phase 1/2 MOMENTUM Study of a Modified Gamma Globin Gene Therapy and Reduced Intensity Conditioning

Michael Grimley, MD[1], Monika Asnani, DM, PhD[2], Archana Shrestha, PhD[1], Sydney Felker, PhD[1,3], Carolyn Lutzko, PhD[1], Paritha I. Arumugam, PhD[1], Scott Witting, PhD[1], Jennifer Knight-Madden, MBBS, PhD[2], Omar Niss, MD[1], Charles T. Quinn, MD[1], Christopher Lo, BS[3], Courtney R. Little, BSN[3], Alisa Dong, PhD[3], and **Punam Malik, MD[1]**

[1]Cincinnati Children's Hospital Medical Center
[2]Caribbean Institute for Health Research
[3]Aruvant Sciences

Speaker disclosures

Dr. Punam Malik:

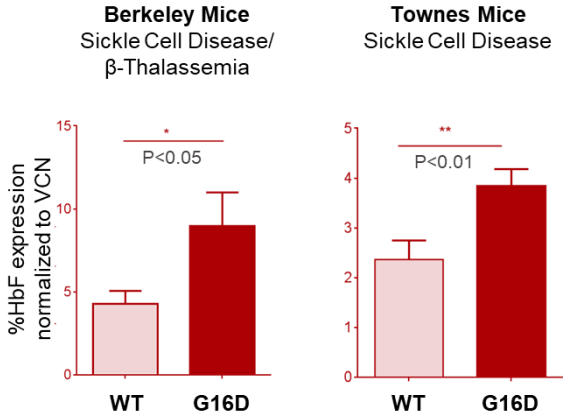
- Consultant and patents/royalties, Aruvant Sciences
- Consultant, Forma Therapeutics
- Patents/royalties, CSL Behring

The MOMENTUM study is a Phase 1/2 trial of ARU-1801 utilizing reduced-intensity conditioning (RIC) in patients with severe SCD

- ARU-1801 is a lentiviral gene therapy that inserts a modified γ-globin gene into autologous CD34+ HSCs to produce HbF^{G16D}
- Preclinical studies in SCD mice indicate high anti-sickling potency of HbF^{G16D}
- We hypothesize ARU-1801 with RIC could lower toxicities and resource utilization relative to myeloablative approaches, allowing expanded access to gene therapy in a broader group of SCD patients
- Updated data on patients in the ongoing Phase 1/2 study (NCT02186418) are presented here

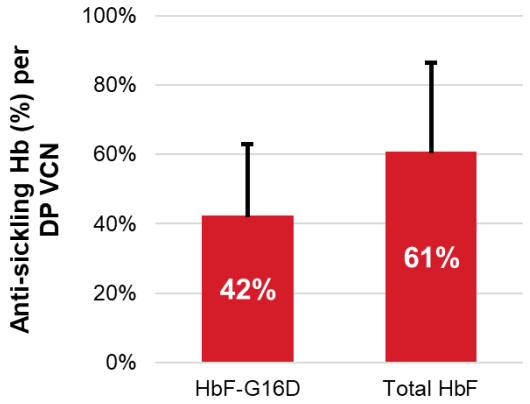
ARU-1801 results in higher anti-sickling globin production per vector copy

Figure 1. SCD murine models: higher HbF expression per VCN seen with HbF^{G16D} vector vs analogous HbF vector



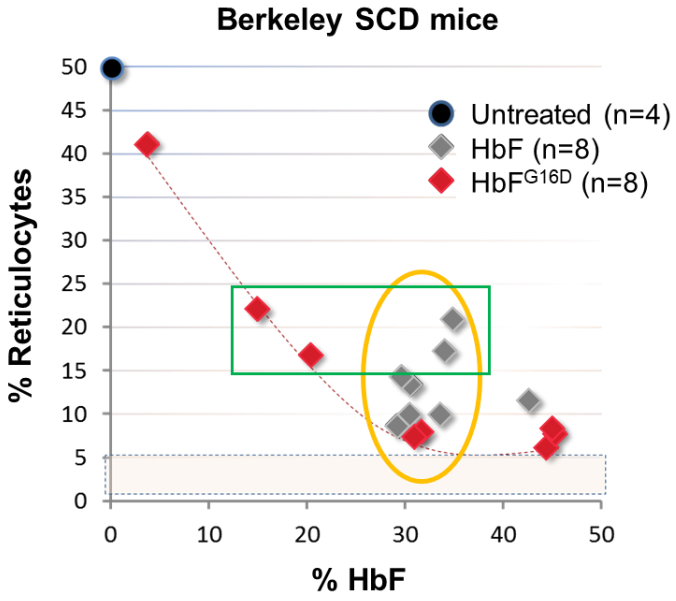
HbF^{G16D} led to 1.5-2x more HbF per vector in well-established SCD mouse models

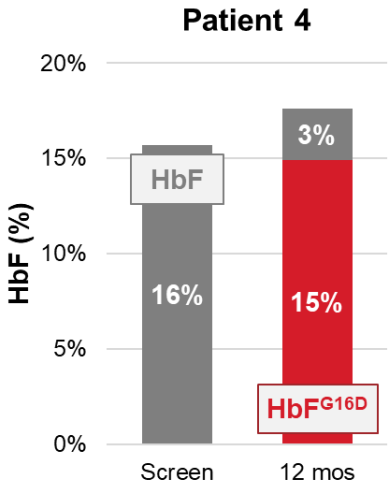
Figure 2. Ph 1/2 (n=4): mean anti-sickling globin per DP VCN (at 24 mos or latest follow-up)



First four patients in Phase 1/2 trial demonstrate relatively high HbF production per vector copy

In preclinical models and patients in this Phase 1/2 clinical trial, HbF^{G16D} shows higher anti-sickling potency than HbF





Similar levels of HbF at baseline HbF^{G16D} at 12 months

12 mo pre-consent ***8 VOEs***

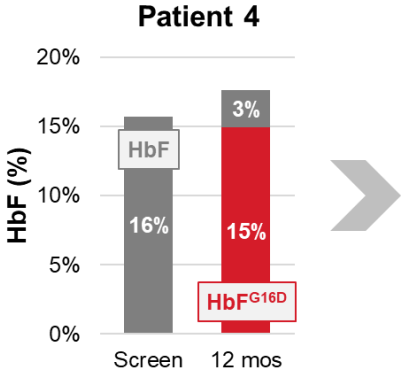
12 mo post-1801 ***0 VOEs***

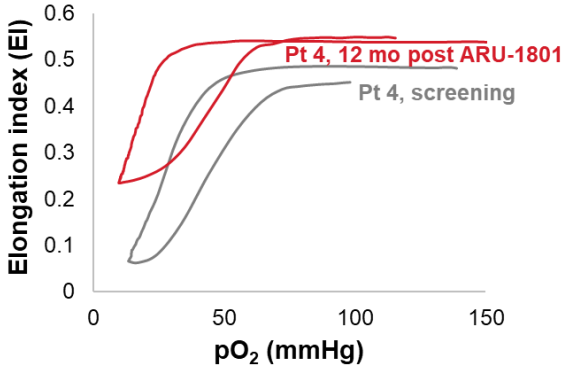
Markedly different clinical phenotype

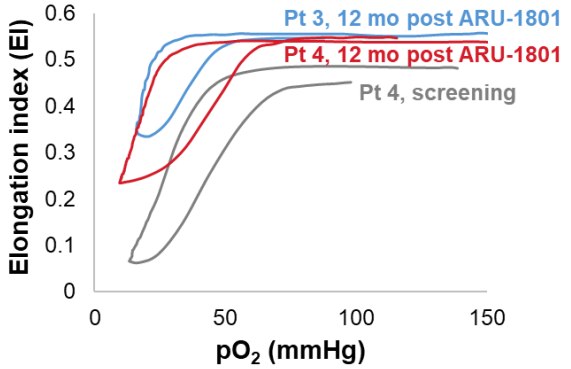
HbF^{G16D} has high anti-sickling potency

Patient 4: Oxygen gradient ektacytometry shows marked improvement in sickling kinetics with 18% HbF^{G16D} at 12 months post ARU-1801 compared to 16% HbF at baseline

Patient 3 vs 4: Oxygen gradient ektacytometry shows similar improvement in sickling kinetics with 18% and 38% HbF, respectively





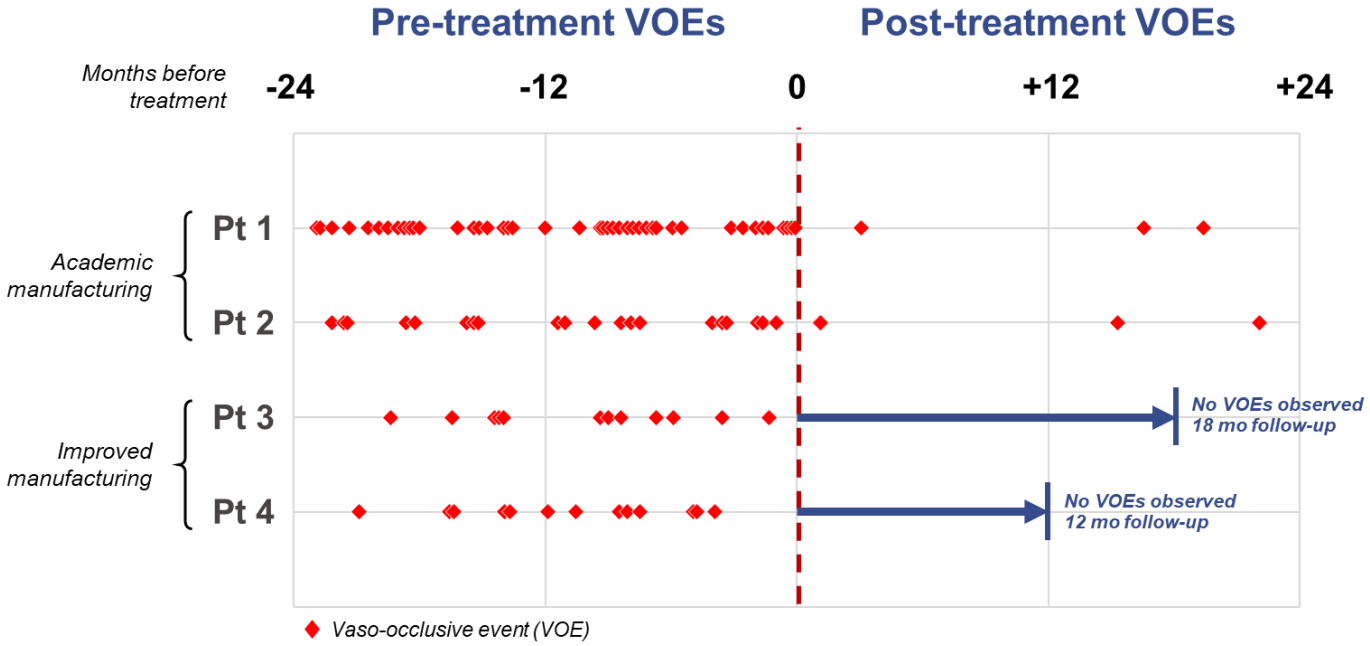


	Point of sickling	% total HbF	%HbF^{G16D}	% F-cells	% HbA
Pt 4, screening	50 mmHg	16%	0	20%	0%
Pt 4, 12 mo	30 mmHg	18%	15%	68%	0%
Pt 3, 12 mo	27 mmHg	38%	26%	96%	0%

Safety profile is consistent with RIC, no related SAEs

	Pt 1	Pt 2	Pt 3	Pt 4
Days of neutropenia	9	7	7	8
Days of thrombocytopenia	13	4	5	4
ARU-1801-related AEs				
Infusion AEs	0	0	0	0
Late AEs	None (48 mo)	None (42 mo)	None (18 mo)	None (12 mo)
Vector insertion	Polyclonal engraftment with no evidence of clonal expansion			
Chemotherapy-related AEs				
Serious	None	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	Cytopenias, mouth pain, diarrhea, nausea, fatigue, elevated LFTs

Significant reductions in VOEs from 24 months prior to consent vs 24 months (or latest follow-up) after treatment with ARU-1801



% VOE reduction	Change in VOEs	% total HbF
93%	43 → 3	28%
80%	20 → 4	15%
100%	12 → 0	37%
100%	13 → 0	18%

Conclusions

- Preclinical and clinical data demonstrate that ARU-1801 can achieve therapeutic levels of anti-sickling Hb at relatively low vector copy number
- HbF^{G16D} levels of 15% with 68% F cells can confer sufficient improvement in RBC function to ameliorate VOEs, supporting the robust anti-sickling potency of this novel fetal hemoglobin
- ARU-1801 has shown:
    - clinically meaningful outcomes with durable engraftment following a single RIC dose of melphalan
    - a promising alternative to therapies requiring myeloablative conditioning