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Sickle Cell Disease: Sickling and Other Hemoglobinopathies

Neil A. Zakai, MD MSc
University of Vermont
Burlington, VT, USA

Based on the North America Presentations by

Julie Kanter, MD
University of Alabama at Birmingham
Birmingham, AL

Jeffrey Lebensburger DO, MSPH
University of Alabama at Birmingham
Birmingham, AL

Robert Liem, MD, MS
Northwestern University
Chicago, IL

Elliott Vichinsky, MD
University of California, San Francisco
Oakland, CA

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Speakers

Neil A. Zakai, MD MSc

Disclosures

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Learning Objectives

- Identify outcomes for novel treatment options for patients with sickle cell disease
- Understand the psychological and end-organ complications in patients with sickle cell disease

CLINICAL CASE

- You are taking care of a 22-year-old female with sickle cell disease (Hemoglobin SS) after a recent pain episode
- She is upset as she is always treated poorly in the Emergency Department when she is in pain
- She asks for your help as this causes distress and lack of trust in the hospital



Audience Response Question

- Do these traumatizing events impact sickle cell disease outcomes?
 - A. No
 - B. Yes





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Self-Efficacy and Stigma in Adults with
Sickle Cell Disease:
An IMPORT database analysis

Stephanie H Guarino, MD, Keshab Subedi, Olusegun Bakare, Charmaine Wright, MD, MSHP,
Lee Pachter, DO, Mary Catherine Beach, MD and Sophie M. Lanzkron, MD

Background, Aims, and Methods

- Background
 - Patients with frequent and chronic pain report significant depression, limitations in daily function, and decreased self-efficacy
 - Experiences of discrimination are associated with poor mental health
- Aim
 - Assess the relationship between SCD stigma, self-efficacy, and other factors
- Methods
 - Cohort of ~290 people with sickling hemoglobinopathies, 15+ years from Maryland and Washington DC, USA
 - 5 relevant surveys used:

Sickle Cell Disease Stigma	Sickle Cell Self-Efficacy Scale	Sickle Cell Self-Care Behaviors
Interpersonal Processes of Care Instrument	Experience of Bias in Medical Settings	

Results

- People with SCD report higher rates of race-based discrimination compared to other Black people
- Increased disease-based discrimination correlated with increased self-reported pain
- Other findings:
 - **Higher trust in institution and older age were associated with higher self-care**
 - **Trust in institution and education level positively associated with self-efficacy**
 - **Stigma associated with lower self-efficacy and higher pain catastrophizing**



Take Home Points

- Discrimination and lack of trust in health care systems are correlated with worse clinical outcomes
- Centrality of compassionate interpersonal communication shows importance of bidirectional relationship between patients and clinicians



CONTINUED CASE

- She has had three admissions for uncomplicated pain crisis in the past year. In the past, she has refused hydroxyurea but you are not sure why.
 - You discuss that she could benefit from a sickle cell modifying therapy.
 - Aside from her pain, she feels like sickle cell has not impacted her life.
 - She also is not aware of any other reasons to consider taking a disease modifying treatment

RELEVANT CLINICAL QUESTION

What should I discuss with my patient about CNS injury in SCD?



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Progressive Silent Cerebral Infarcts Are Prevalent in Adults with Sickle Cell Anemia but Moderate-Severe Cognitive Abnormalities Are Independent of Preexisting Silent Cerebral Infarcts

Ibrahim Musa Idris, MBBS, MPH, FMCPATH, Dalha H Gwarzo, MBBS, FMCPATH, Shamsu Iguda, MBBS, Faruk Aminu, MBBS, Mustapha Shuaibu Hikima, MBBS, FMCRad, Mohammed Kabir Saleh, MBBS, FMCRad, Mohammad Abba Suwaid, MBBS, FMCRad, Aliyu Ibrahim, MBBS, FWACP, Hauwa Ibrahim, MBBS, FMCPATH, Shehu Kana, MBBS, FWACP, Rabia Abubakar Haruna, RN, Jamil Aliyu Galadanci, MSc, Nafiu Hussain, PhD, Mark Rodeghier, PhD, Hyacinth I Hyacinth, MD, PhD, MPH¹, Allison A. King, MD, PhD, MPH and Michael R. DeBaun, MD, MPH

Neurological morbidities in adults with Sickle Cell Disease are not adequately documented

Silent Cerebral Infarct: Absence of neurological deficit as confirmed by neurologist. MRI lesion showing hyperintensity ≥ 3 mm in diameter and visible in at least two planes of T2-weighted FLAIR images (axial and coronal).

- Children with Sickle Cell Disease have demonstrated an association between cognitive abnormalities and stroke or silent infarcts
- Silent infarcts are associated with future overt or silent infarcts in children
- In adults, information is inadequate about the relationship between silent infarcts and cognition

Objective

- Describe SCI prevalence, recurrence rate, and association with cognitive impairment

Longitudinal CNS cohort in adults with SCD in Nigeria

- 246 young adults
 - 16+ years of age
- Baseline and 12-month studies
 - MRA/MRI
 - Cognition assessment
- Prevalence of silent infarcts (SCI)
 - 60% (n=148) of young adults

	Overall, N=246	SCI, n- 148	No SCI, n=98	P- value
Age	22.7 ± 5.0	23.2± 5.0	21.8±5.0	0.039
Female	141(57.72)	80 (54.05)	61 (62.24)	0.171
HU use	37 (15.10)	26 (17.57)	11 (11.34)	0.183
HbF	7.14±5.2	6.42±5.0	8.22±5.3	0.008

Longitudinal CNS cohort in adults with SCD in Nigeria

- Repeat imaging in 106 participants
 - 26% versus 8% had new SCI in those with baseline versus those without baseline SCI
- Cognitive outcomes
 - Moderate to severe cognitive defects common in attention & executive function, episodic memory, working memory, and processing speed in general
 - SCI not associated cross-sectionally with cognitive defects in this population



Take Home Points

- Adult SCD patients have a high prevalence of silent infarcts
- In adults, significant cognitive abnormalities exist but are independent of infarct status
- High rate of SCI occurrence in adults especially with pre-existing SCI



CONTINUED CASE

- After discussing how SCD may affect her organ function long-term, she agrees to start a sickle cell disease modifying therapy
- She has been told about HU in the past.
 - She is worried about the affects of HU on fertility
- She knows Voxelotor increases Hb levels but wonders about the clinical benefits

RELEVANT CLINICAL QUESTION

What clinical benefit may Voxelotor have in SCD?





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Real-World Effectiveness of Voxelotor for the Treatment of Sickle Cell Disease Group and Pediatric Subgroup Analyses of Effects on Transfusions, Vaso-occlusive Crises, and Hospitalizations

Nirmish Shah, MD; Thokozeni Lipato, MD; Thomas E. Delea, MSIA; Alexander Lonshteyn, PhD; Derek Weycker, PhD; Andy Nguyen, PhD; Anne Beaubrun, PhD; Ofelia Alvarez, MD

Introduction and Objective

- **Voxelotor** is a first-in-class sickle hemoglobin polymerization inhibitor that targets the underlying pathophysiology of SCD.
- Studies indicate that voxelotor **increases hemoglobin** and **reduces markers of hemolysis**
- **OBJECTIVE:** To determine the real-world rates of transfusions, VOCs, and hospitalizations among people with SCD initiating voxelotor

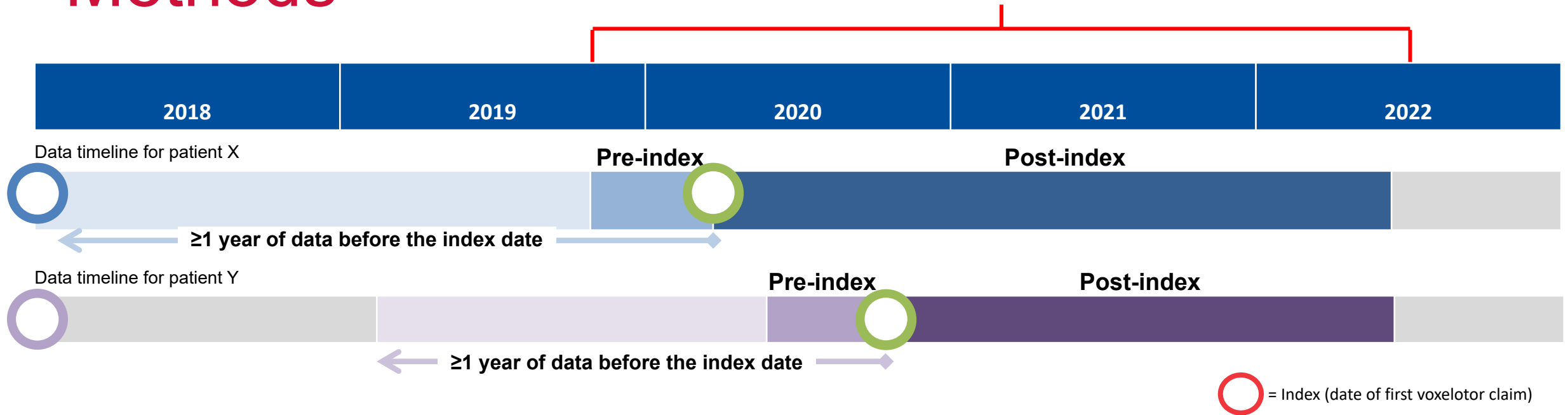


Methods

Symphony Health
Dataverse Database



Healthcare data, including medical and pharmacy claims, for patients aged ≥ 4 years with SCD who started voxelotor



- This study evaluated annualized outcomes per patient-year in the pre - (**3 months prior**) and compared it to post-index (time after first prescription) period.



Study Population

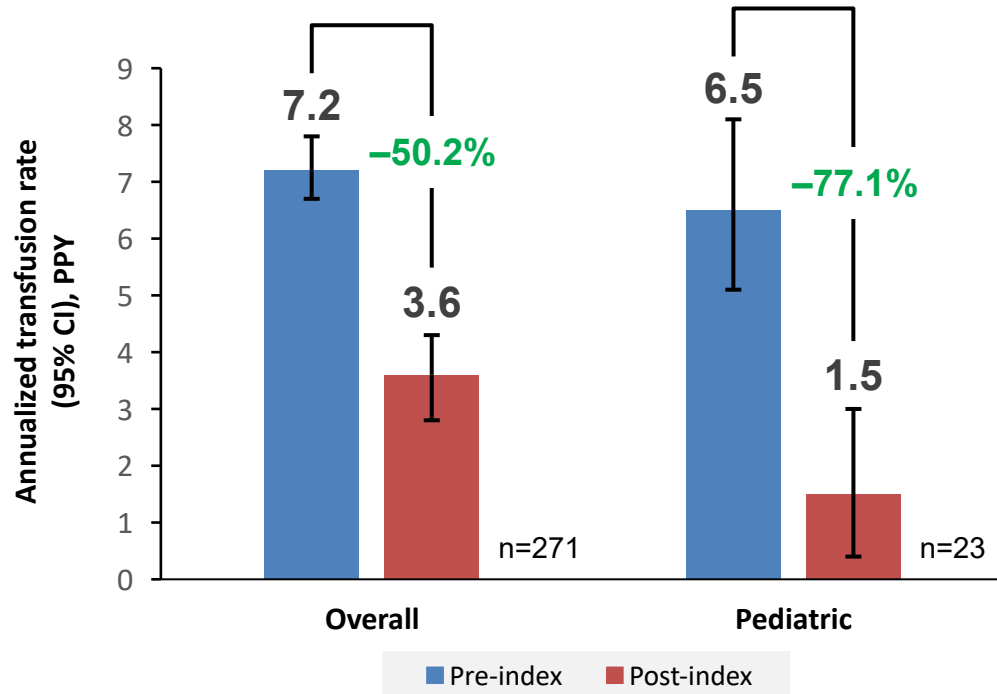
Baseline Patient Demographics and Duration of Follow-up

	Overall N=4521	Pediatric n=830
Age, mean (range), years	33.4 (4-80)	13.2 (4-17)
Age group, n (%)		
4 to 11 years	170 (3.8)	170 (20.5)
12 to 17 years	660 (14.6)	660 (79.5)
18+ years	3691 (81.6)	-
Sex, n (%)		
Female	2658 (58.8)	434 (52.3)
Male	1863 (41.2)	396 (47.7)
Follow-up, median (Q1,Q3), days	78 (45, 157)	82 (45, 159)
Follow-up length >1 year, n (%)	321 (7.1)	67 (8.1)

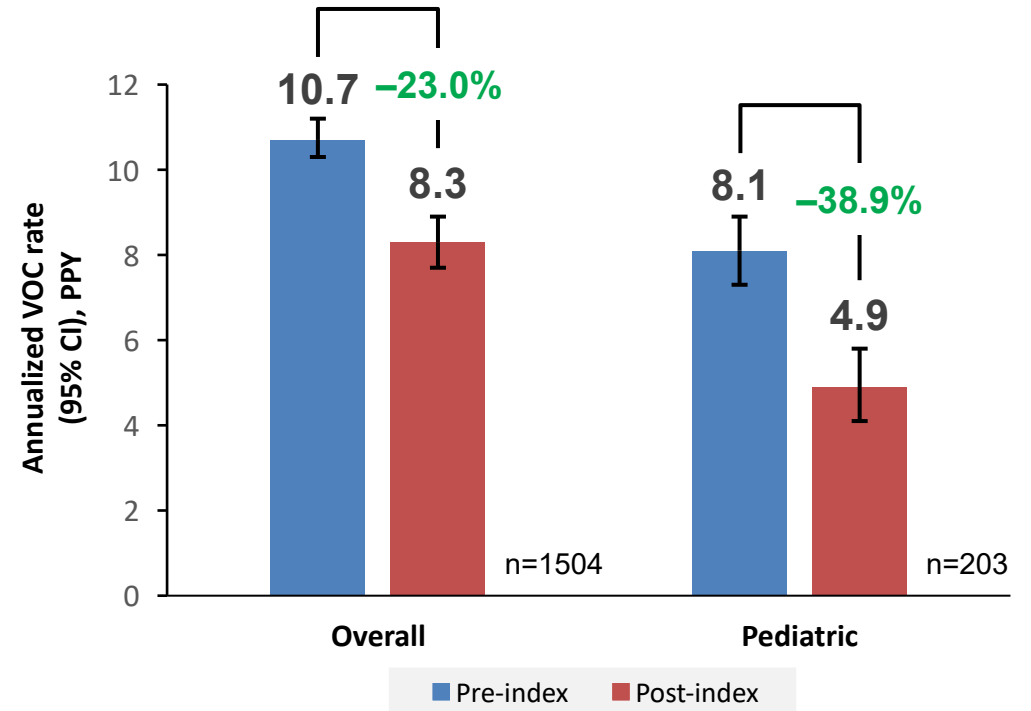
Data cutoff: June 2022.
Q, quartile; SCD, sickle cell disease.

Change in Number of Transfusions and VOCs

People with ≥ 1 Transfusion



People with ≥ 1 VOCs

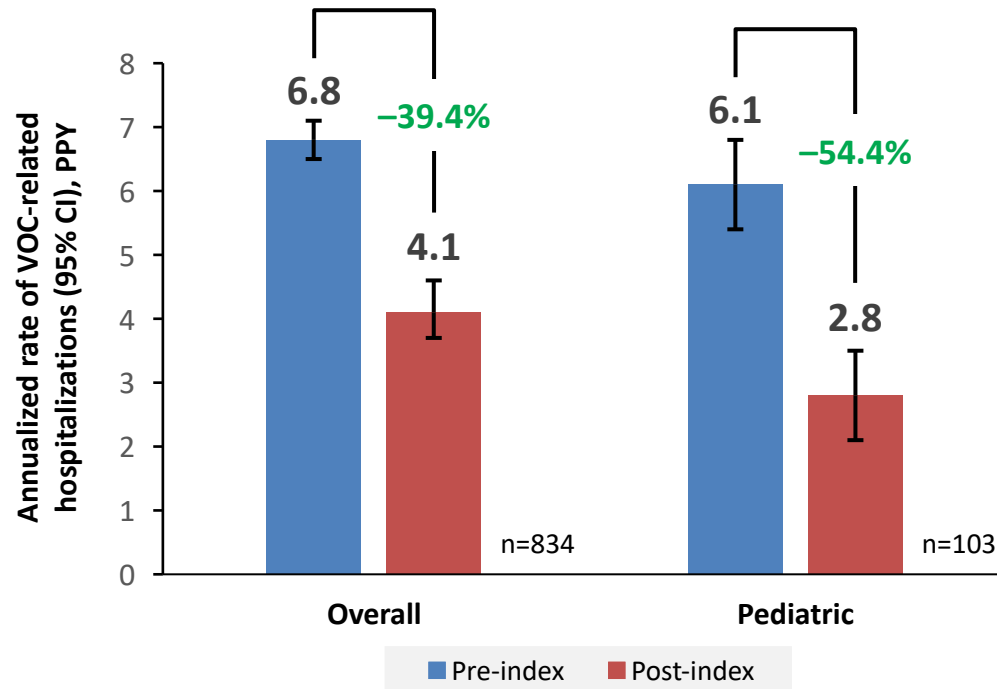


Compared with those in the 3-month pre-index period, lower annualized rates of transfusions and VOCs were observed in the post-index period for the overall population and the pediatric subgroup.

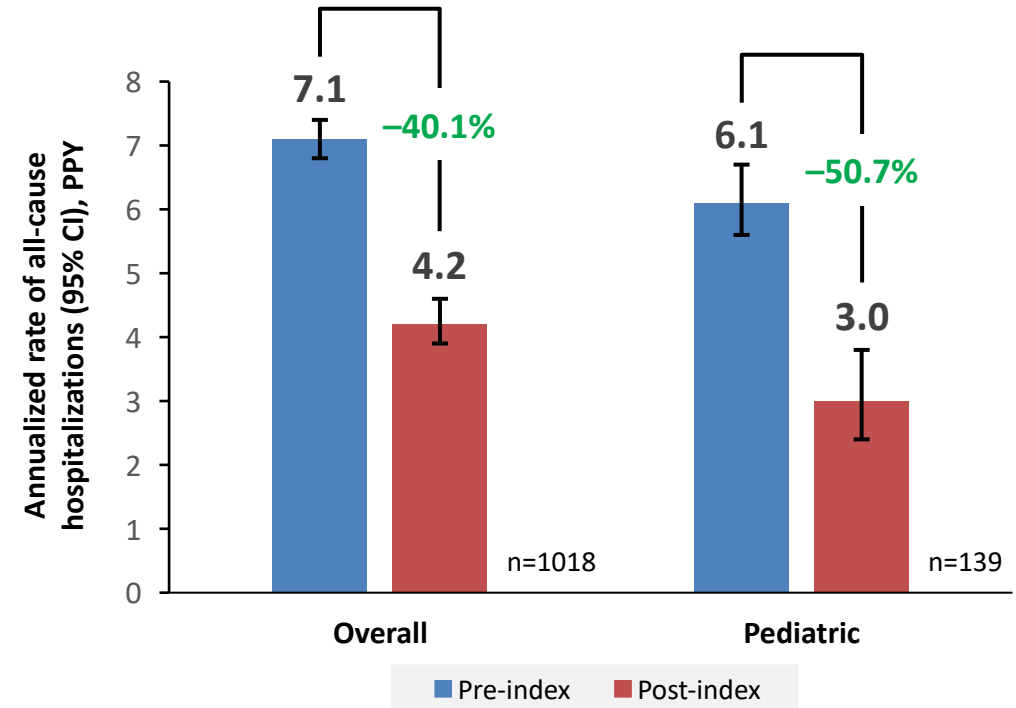
Pre-index refers to the 3-month period before and on the day of the patient's first voxelotor claim. Post-index refers to the period from 1 day after the patient's first voxelotor claim to the end of continuous voxelotor treatment up to June 2022. PPY, per patient-year; VOC, vaso-occlusive crisis.

Change in Number of Hospitalizations

Patients with ≥ 1 VOC-Related Hospitalization



Patients with ≥ 1 All-Cause Hospitalization



Compared with the 3-month pre-index period, lower annualized rates of hospitalizations were observed in the post-index period for the overall population and the pediatric subgroup.

Pre-index refers to the 3-month period before and on the day of the patient's first voxelotor claim. Post-index refers to the period from 1 day after the patient's first voxelotor claim to the end of continuous voxelotor treatment up to June 2022. PPY, per patient-year; VOC, vaso-occlusive crisis.

Take Home Points

Voxelotor treatment was associated with a reduction in frequency of transfusions, VOCs, and hospitalizations

Children benefited as well – justifying use in this population

Awaiting full data analysis



CONTINUED CASE

- She is now interested in starting a disease modifying therapy.
- She also wonders about whether her brother (who also has SCD) should be on a treatment
 - He suffers from pain but his episodes of priapism have increased over the last several years



Audience Response Question

- What SCD modifying therapies help reduce priapism?
 - A. Hydroxyurea
 - B. Voxelator
 - C. Crizanlizumab
 - D. Both Hydroxyurea and Voxelator





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Interim Analysis of a Phase 2 Trial to Assess the Efficacy and Safety of Crizanlizumab in Sickle Cell Disease Patients With Priapism (SPARTAN)

Alan Anderson, Fuad El Rassi, MD, Michael R. DeBaun, MD, MPH, Modupe Idowu, MD, Julie Kanter, MD, Soheir Adam, MD, FRCPath, Susanna Curtis, MD, PhD, Darla Liles, MD, Biree Andemariam, MD, Morgan L. McLemore, Robert Sheppard Nickel, MD, MSc, Poornima Ramadas, MD, Jincy Paulose, MD, Dramane I Laine, Mahmudul Khan, Deepika S. Darbari, MD and Arthur L. Burnett, MD, MBA

Background

- Priapism occurs in approximately 40% of men with SCD
- There is no SCD-modifying drug known to reduce priapism
- Crizanlizumab is a monoclonal antibody that binds and blocks P-selectin, a key mechanistic component of the vaso-occlusion process
- Interim analysis of the SPARTAN trial (NCT03938454) assessing the efficacy and safety of crizanlizumab on priapism

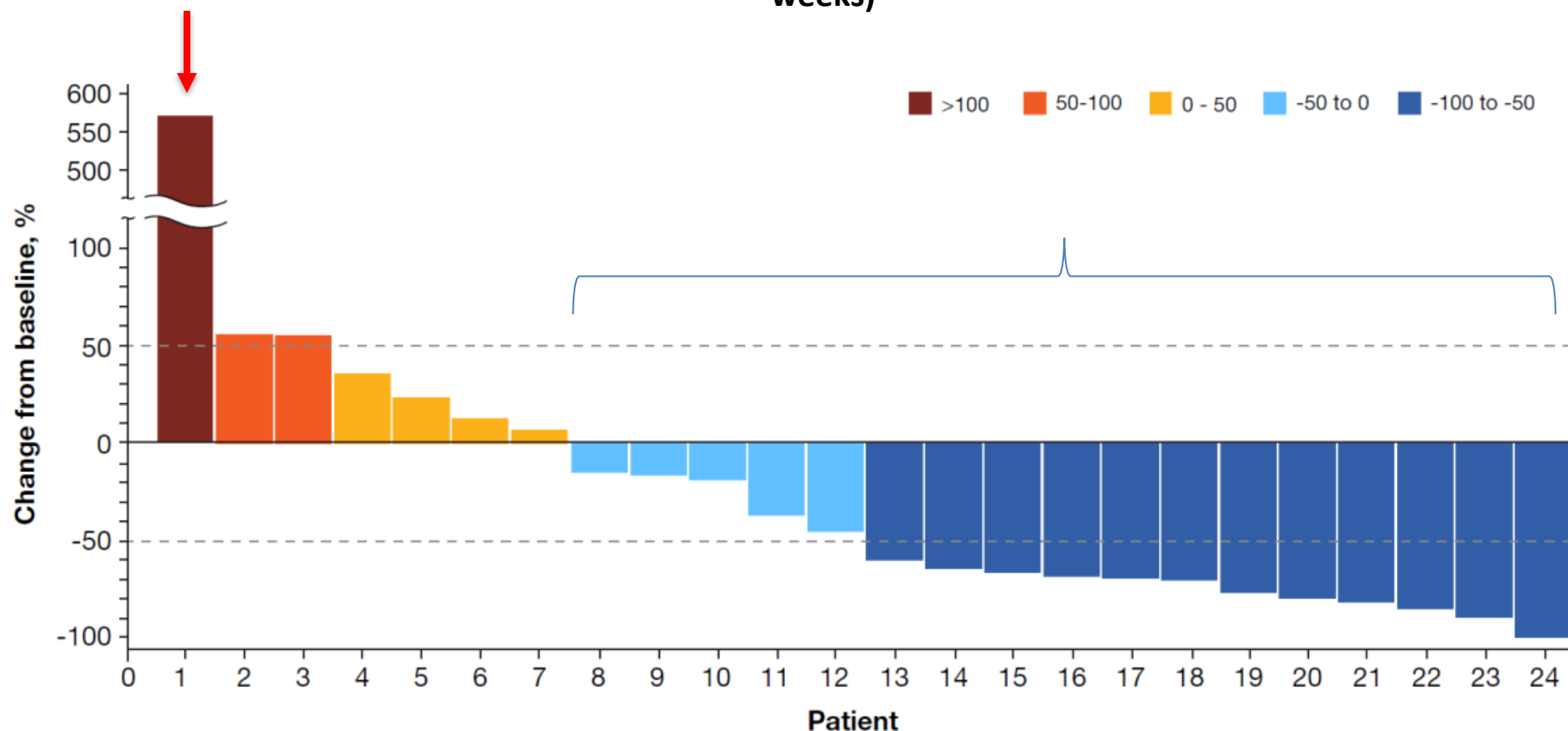
SCD, sickle cell disease.

References: 1. Alvaia MA, et al. *Einstein (Sao Paulo)*. 2020;18:eAO5070. 2. Idris IM, et al. *Blood Adv*. 2020;4(14):3277-3283. 3. Crane GM, Bennett NE Jr. *Anemia*. 2011;2011:297364. 4. Anele UA, et al. *Blood*. 2015;125(23):3551-3558. 5. Adakveo [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2021.



RESULTS: 71% of Patients Reported a Reduction in Priapic Events and 53% Reduction in Frequency of Priapic Events

Percent change from baseline in priapic events by patient (adjusted for 26 weeks)



Take Home Points

- Patients with SCD-related priapism treated with crizanlizumab experienced a 53% reduction in priapic events by week 26
 - Trend toward improved efficacy with a longer treatment period and in patients with a higher number of priapic events at baseline
- Final results of the SPARTAN trial with longer exposure data on more patients can be expected to provide reliable conclusions regarding the efficacy of crizanlizumab in decreasing priapism in SCD

Clinical Case Continued: 24 months later

- Your patient opted to start hydroxyurea
- She and her husband are doing well and have wonderful news that they will be expecting a child
- Importantly, she stopped her hydroxyurea when she knew she was pregnant (and has been receiving monthly transfusions)
- She wants to know about any issues that should concern her having SCD

RELEVANT CLINICAL QUESTION

What are potential risks for SCD during pregnancy





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Sickle Cell Disease-Specific Blood Pressure Thresholds for Hypertensive Disorders of Pregnancy: A Multinational Study

Macy L. Early, BA, A. Kinga Malinowski, MD, MSc, FRCSC, Marissa Solow, MD,
Ahizechukwu Eke, MBChB, PhD, Sana Saif Ur Rehman, MD, Nadine Shehata, MD,
FRCPC, MSc, Kevin H.M. Kuo, MD, MSc, FRCPC and Lydia H. Pecker, MD

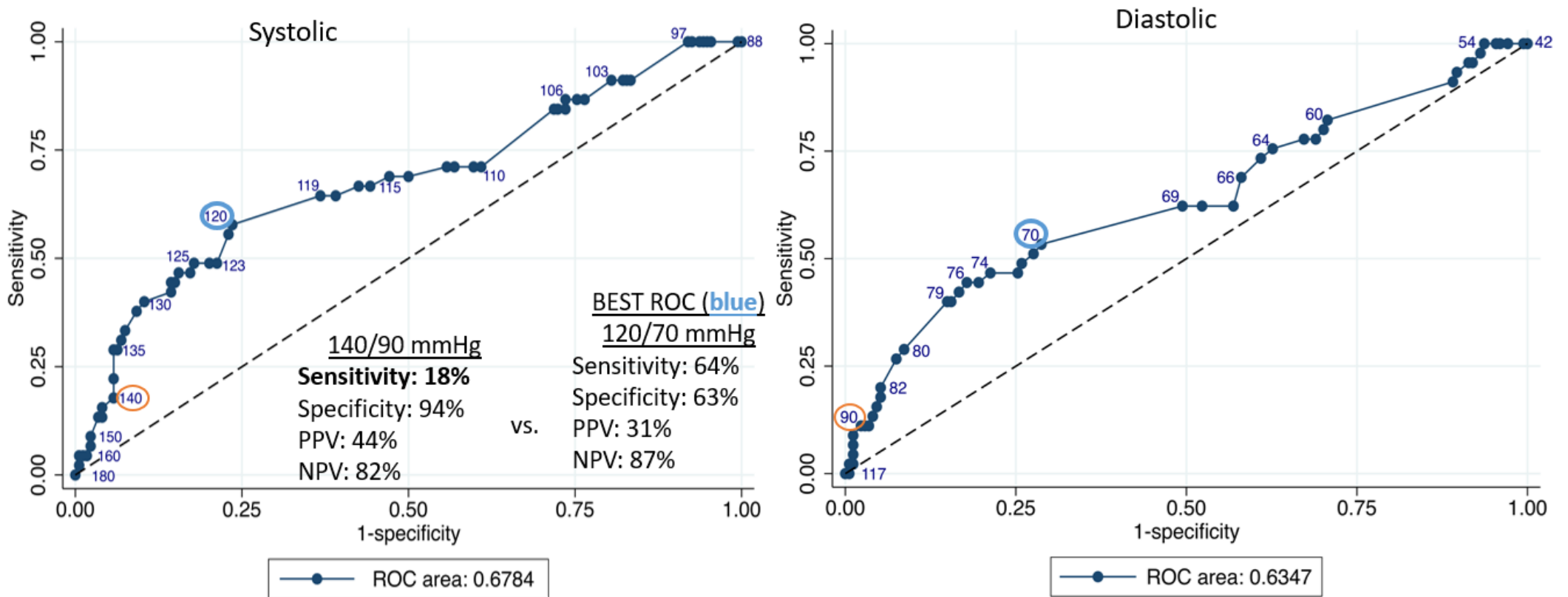
Background

- Pregnancy in SCD is high-risk
 - 26 times the risk of mortality and 7 times the risk of Severe Maternal Morbidity
- Hypertensive disorders of pregnancy are common
 - Gestational hypertension: isolated blood pressure elevations
 - Preeclampsia: elevated blood pressure + signs of end organ damage
 - Eclampsia: elevated blood pressure + seizure
- **Issue**: Blood Pressure is lower in SCD patients
- Objective: To evaluate the sensitivity and specificity of blood pressure thresholds in identifying preeclampsia in pregnant people with SCD (as measured by new or worsening proteinuria)

Less than half of 54 patients with new or worsening proteinuria received a preeclampsia diagnosis

	New or worsening proteinuria N=54	No or stable proteinuria N=238	P-values
Diagnosis with hypertensive disorder of pregnancy			
Gestational HTN diagnosis, N(%)	3 (6)	9 (4)	<.001
Preeclampsia diagnosis, N(%)	21 (39)	6 (3)	<.001
Eclampsia diagnosis, N(%)	1 (2)	0 (0)	.19
Pregnancy outcomes			
Preterm delivery <37 wks, N(%)	31 (57)	52 (22)	<.001
Extreme preterm <34 wks, N(%)	10 (19)	20 (8)	.03
Birth weight <10% predicted, N(%)	15 (28)	65 (28)	.95

120/70 is more accurate than 140/90 mmHg in SCD pregnancy to identify new or worsening proteinuria



*Pregnancies with last outpatient BP and proteinuria, N=45

Take Home Points

- Patients with new or worsening proteinuria are not receiving a pre-eclampsia diagnosis based on using normative BP.
- 120/70 mmHg was the optimal threshold and should be studied prospectively for validation and refinement.

CLINICAL CASE

- Her first pregnancy resulted in a premature birth (30 weeks) complicated by pre-eclampsia
- While deciding whether she wants more children, she wants to know about methods and concerns with contraceptive care

RELEVANT CLINICAL QUESTION

What contraceptive device should I use in SCD?





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Hormonal Contraceptive Use and Association with Thromboembolism in Women with Sickle Cell Disease

Natasha Bala, MD, Joseph R. Stanek, MS, Sara K. Vesely, PhD, Robert M. Cronin, MD, Susan E. Creary, MD, MSc, Andrea H. Roe, MD, MPH Wendy Xu, PhD, Sarah H. O'Brien, MD, MSc

Background

- Limited safety data on hormonal contraceptive use in women with SCD
- US Medical Eligibility Criteria, 2016. SCD Recommendations for Women

Type of contraceptive	Category
Progestin-only contraceptive (POC)	1 (no restrictions)
Combined hormonal contraceptive (CHC)	2 (can be used if benefits>risks)

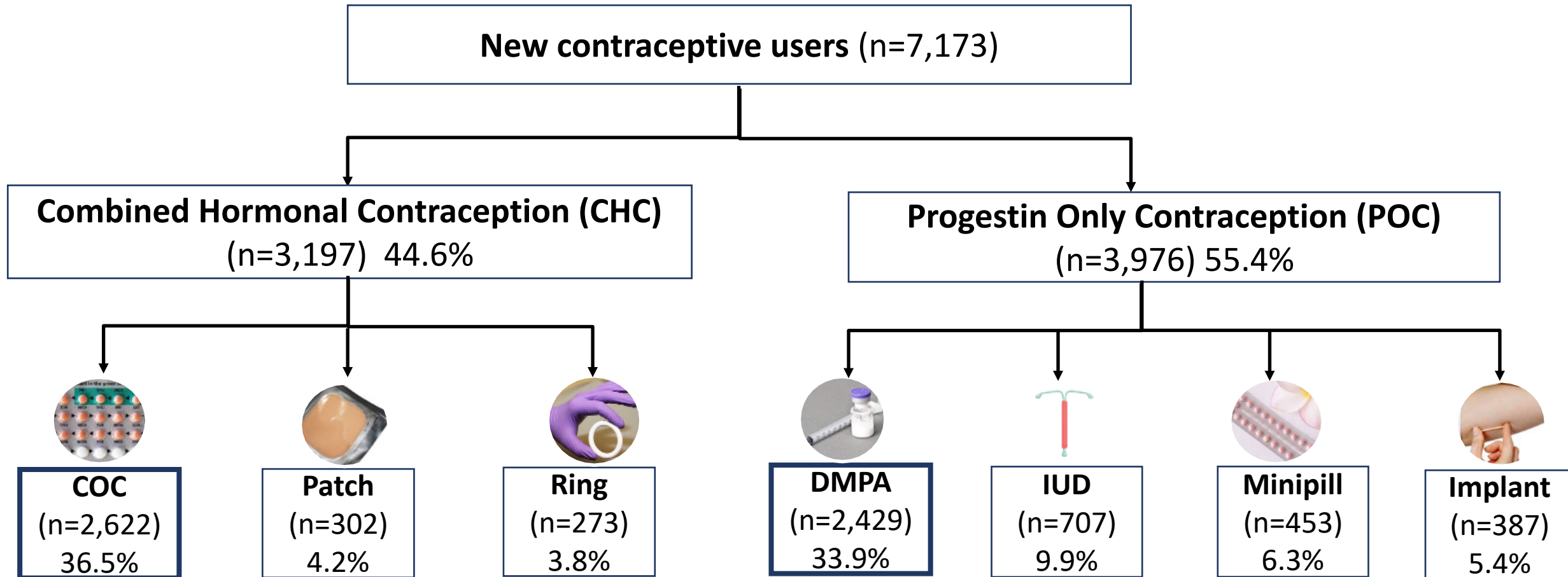
- Depot medroxyprogesterone acetate (DMPA)
 - Associated with an increased risk of thrombosis in the general population

Aims and Methods

- Aims
 - To determine patterns of hormonal contraceptive use
 - Evaluate risk of thromboembolism (TE) during the first year of contraception in women with SCD
- **Data source**
 - Centers for Medicare and Medicaid Services Analytic eXtract (2006-2018)
- **Study population**
 - Women of reproductive age (12-44 years) with ≥ 3 ICD codes for SCD and at least one prescription for a new contraceptive



Patterns of contraception use in women with SCD



TE events

- 126 (1.8%) new users developed a TE event in the 1st year of hormonal contraceptive use
 - TE event rate was 21 events per 1000 person years
- PE (49.2%), DVT (40.5%), Stroke (4%), MI (1.6%), multiple TE's (4.8%)
 - Median time to TE from contraception use was 170 days (IQR:70-257 days)
- **No difference in adjusted events for CHC (Level 2) and POC (Level 1)**

	Event rate per 1000 women-years (95% CI)	Adjusted* HR (95% CI)	P-value
CHC (45 Events)	17.2 (12.9-23.1)	0.84 (0.58-1.22)	0.36
POC (81 Events)	24.7 (19.9-30.7)	Reference	-

**Adjusted for SCD severity and age*



TE rates

Type of contraceptive	Rates of TE/1000 person-years	Unadjusted HR (95% CI)	P-value	Adjusted* HR (95% CI)	P-value
CHC formulation		<i>*Adjusted for SCD severity and age</i>			
OCP	15.2 (10.8-21.4)	Reference	-	Reference	-
Transdermal patch	33.7 (16.8-67.3)	2.21 (1.02-4.78)	0.0436	2.45 (1.13-5.34)	0.0240
Vaginal ring	19.5 (7.3-51.9)	1.27 (0.45-3.57)	0.64	1.14 (0.40-3.24)	0.80
POC formulation					
IUD	42.0 (28.1-62.6)	Reference	-	Reference	-
POP	11.4 (4.3-30.4)	0.27 (0.09-0.78)	0.0159	0.38 (0.13-1.11)	0.08
DMPA	21.5 (16.0-28.9)	0.51 (0.31-0.84)	0.0084	0.67 (0.41-1.11)	0.12
Implant	29.2 (15.2-56.2)	0.70 (0.32-1.50)	0.35	0.97 (0.45-2.09)	0.94

Higher risk women may have non-random selection of contraception

Take Home Points

- Combined OCP and DMPA were most frequently used contraceptives
- 1.8% users had a new diagnosis of TE
 - 21 TE events per 1000 person-years (this is higher than general population)
- Results potentially confounded by indication
 - Higher risk women placed on perceived 'lower' risk options
 - Supports clinical equipoise for studying OCP use in SCD



CLINICAL CASE: 1 month later

- Your patient wants to discuss curative options
- She perform HLA typing and she does not have any suitable donors
- She wants to know more about gene therapy

RELEVANT CLINICAL QUESTION

What are the current outcomes in gene therapy?



Gene therapies for SCD discussed at ASH 2022

- Three Gene Therapy Presentations at ASH 2022
 - OTQ923
 - Exa-Cel
 - Lovo-Cel





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Treatment of Individuals with Severe Sickle Cell Disease with OTQ923, an Autologous, *Ex Vivo*, CRISPR/Cas9-Edited, CD34+ Hematopoietic Stem and Progenitor Cell Product, Leads to Durable Engraftment and Fetal Hemoglobin Induction

Akshay Sharma, MBBS, Jaap Jan Boelens, MD, PhD, Maria I. Cancio, MD, Jane S Hankins, MD, MS, Prafulla A Bhad, MSc, Andrew Lewandowski, PhD, Xiaojun Zhao, PhD, Shripad Chitnis, PhD, Radhika Peddinti, MD, Yan Zheng, MD, PhD, MS, Neena Kapoor, MD, Fabio Ciceri, MD, Jianping Yuan, PhD, Vionnie W. Yu, PhD, Susan C. Stevenson, Serena De Vita, MD, PhD and James LaBelle, MD, PhD

Study design: Phase I/II study (NCT04443907) of OTQ923 in individuals (aged 2–40 years) with severe SCD.

*Cas9–sgRNA (gRNA68) RNP targets the *HBG1/HBG2* promoters on chr 11

Participants had at least one of the following indicators of disease severity:

- ≥3 episodes of vaso-occlusive crisis
- ≥2 episodes of acute chest syndrome
- Recurrent priapism
- History of prior stroke
- Need for chronic transfusions or red cell alloimmunization

Trial objectives

- Safety and tolerability (AEs and SAEs, vital signs, lab values, ECGs)
- Time to neutrophil engraftment^a
- HbF induction

^aTime to neutrophil engraftment was defined as the time to reach an absolute neutrophil count ≥500 cells/μL for 3 consecutive days. AE, adverse event; ECG, electrocardiogram; HbF, fetal hemoglobin; SAE, serious AE; SCD, sickle cell disease.

Phase I/II study (NCT04443907) of OTQ923: Participant demographics and disease severity

	Participant 1	Participant 2
Age at screening, years	22	21
Sex	Male	Male
SCD genotype	β^S/β^S	β^S/β^S
SCD-related symptoms prior to enrollment	Six episodes of ACS over the prior 10 years, and history of a silent cerebral infarct, retinopathy, and priapism	Five vaso-occlusive episodes, three episodes of ACS, and a silent cerebral infarct during the prior 19 years
SCD treatment ongoing at study enrollment	Chronic blood transfusions for primary stroke prevention, hydroxyurea	Hydroxyurea

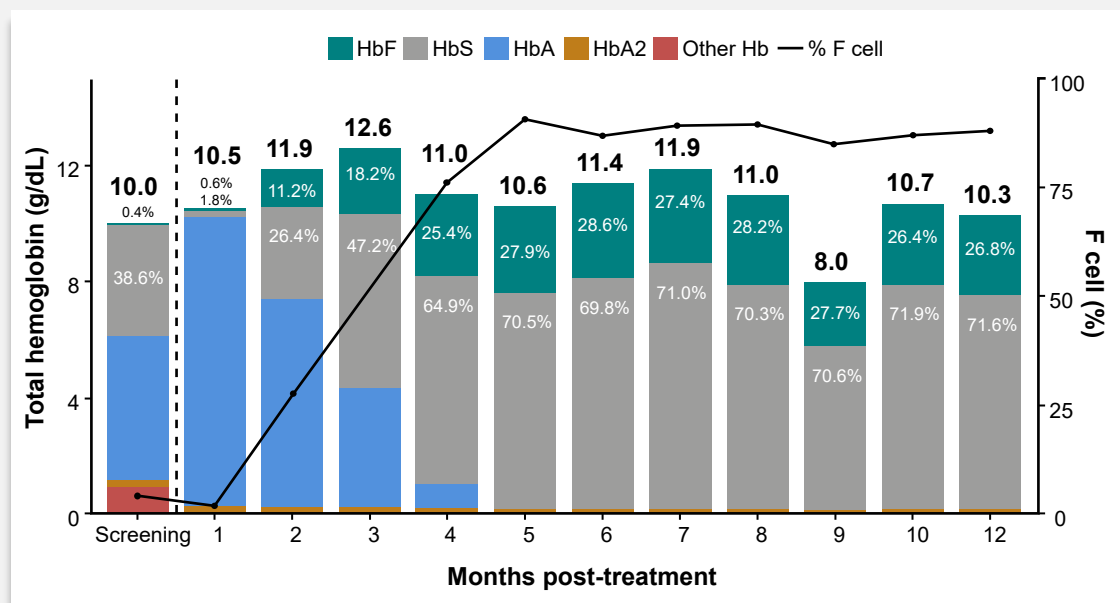
ACS, acute chest syndrome; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

Phase I/II study (NCT04443907) of OTQ923: Total Hb and HbF increased and were sustained over time with no transfusions needed post-engraftment

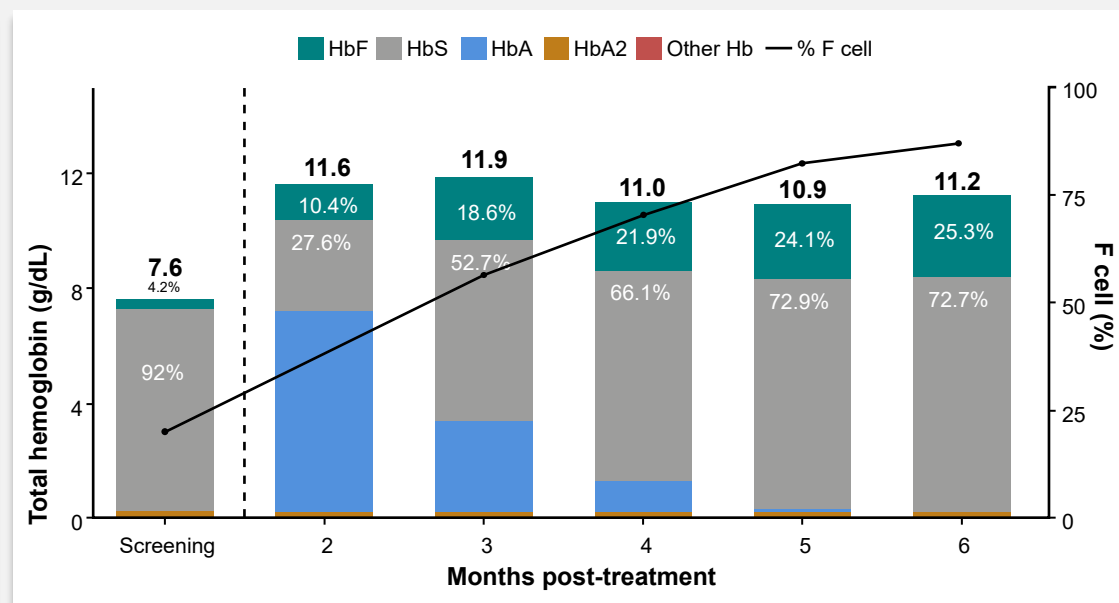
- Pancellular HbF expression (overall <30%) was apparent in both participants.

Total Hb levels and Hb fractionation^a (HbF in green; HbS in gray)
Line graphs represent the percentages of F-expressing red blood cells over time

Participant 1



Participant 2



^aData were collected locally.

Hb, hemoglobin; HbA, adult hemoglobin; HbA2, minor adult hemoglobin; HbF, fetal hemoglobin; HbS, sickle hemoglobin.

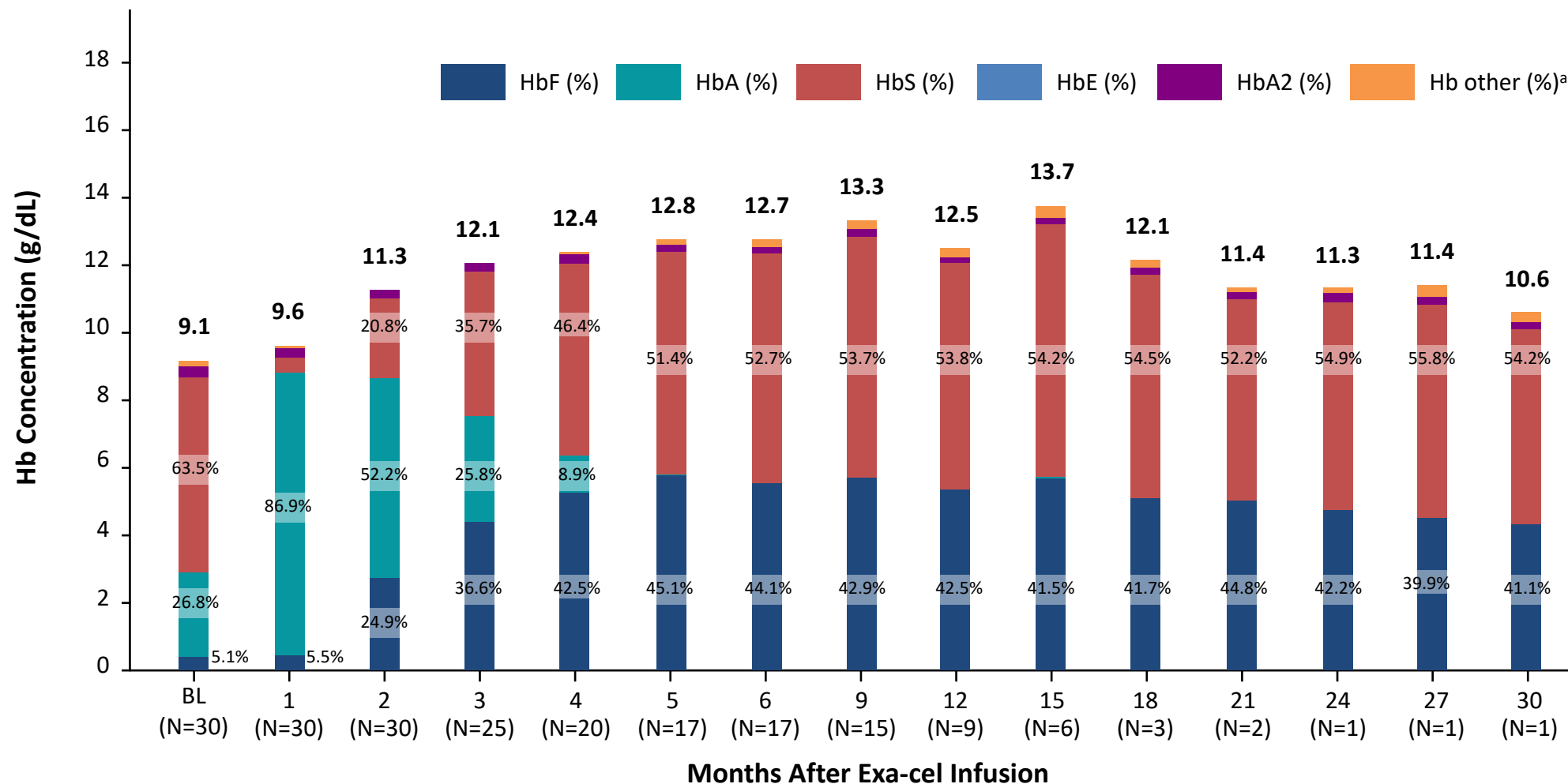


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Single Dose of Exagamglogene Autotemcel (Exa-cel) in SCD

Haydar Frangoul, MD, Franco Locatelli, MD, Monica Bhatia, MD, Markus Y. Mapara, MD, PhD, Lyndsay Molinari, MD, Akshay Sharma, MBBS, Stephan Lobitz, MD, Mariane de Montalembert, MD, PhD, Damiano Rondelli, MD, Martin Steinberg, MD, Mark C. Walters, MD, Suzan Imren, MD¹, Lanju Zhang, PhD, Anjali Sharma, MD, Yang Song, PhD, Christopher Simard, MD, William Hobbs, MD, PhD and Stephen Grupp, MD

Single Dose of Exagamglogene Autotemcel (Exa-cel) in SCD: Meaningful Increases in HbF (>20%) That Occurred Early and Were Sustained Over Time



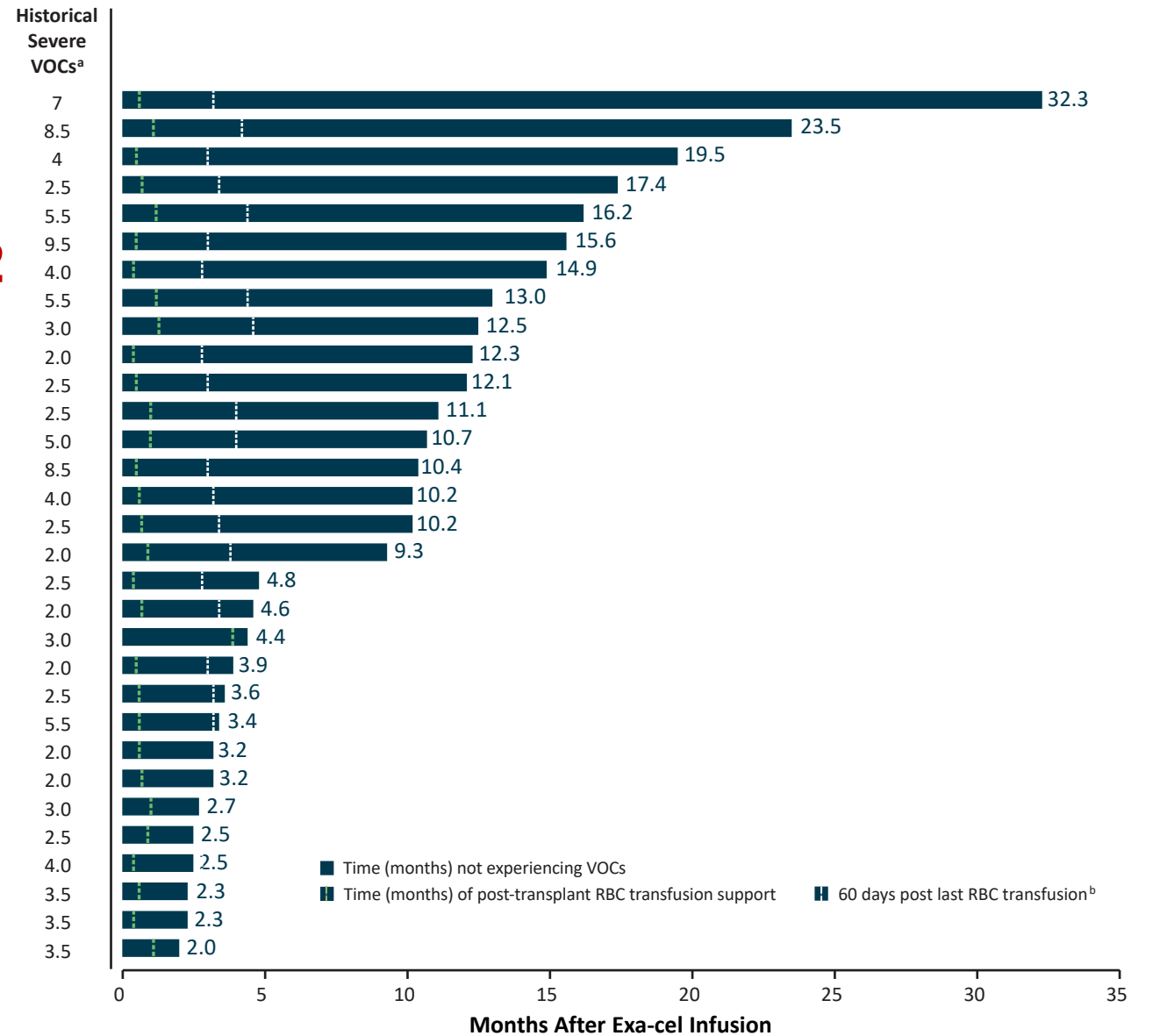
BL, baseline; Hb, hemoglobin; HbA, adult hemoglobin; HbA2, hemoglobin alpha 2; HbE, hemoglobin E; HbF, fetal hemoglobin; HbS, sickle hemoglobin; SCD, sickle cell disease.

Bars show mean Hb (g/dL). Labels indicate mean proportion of HbS and HbF as a percentage of total Hb. Mean total Hb concentrations are shown directly above bars.

^a Hb adducts and other variants.

Single Dose of Exagamglogene Autotemcel (Exa-cel) in SCD: treatment resulted in all patients being VOC-Free as of February 2022 Data Cut-off

- **Time (months)** since exa-cel infusion is indicated by the dark bar
- 31 of 31 patients were **VOC-free** after exa-cel infusion (duration from 2.0 to 32.3 months)



Each row in the figure on the right represents an individual patient.

^aPre-study severe VOCs annualized over 2 years; ^bPatients are evaluated for elimination of VOCs starting 60 days after their last transfusion.

RBC, red blood cell; SCD, sickle cell disease; VOC, vaso-occlusive crisis..



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Lovo-cel (bb1111) Gene Therapy for Sickle Cell Disease: Updated Clinical Results and Investigations into Two Cases of Anemia from Group C of the Phase 1/2 HGB-206 Study

Mark C. Walters, MD, Alexis A. Thompson, MD, MPH, Janet L. Kwiatkowski, MD, MSCE, Suhag Parikh, MD, Markus Y. Mapara, MD, PhD, Stacey Rifkin-Zenenberg, DO, Banu Aygun, MD, Kimberly A. Kasow, DO, Alex Miller, BS, Lixin Zhang, PhD, Anjulika Chawla, MD, Elizabeth R. Macari, PhD, Francis J. Pierciey Jr., MSc, John F. Tisdale, MD and Julie Kanter, MD

Lovo-cel HGB-206 Group C: Safety profile

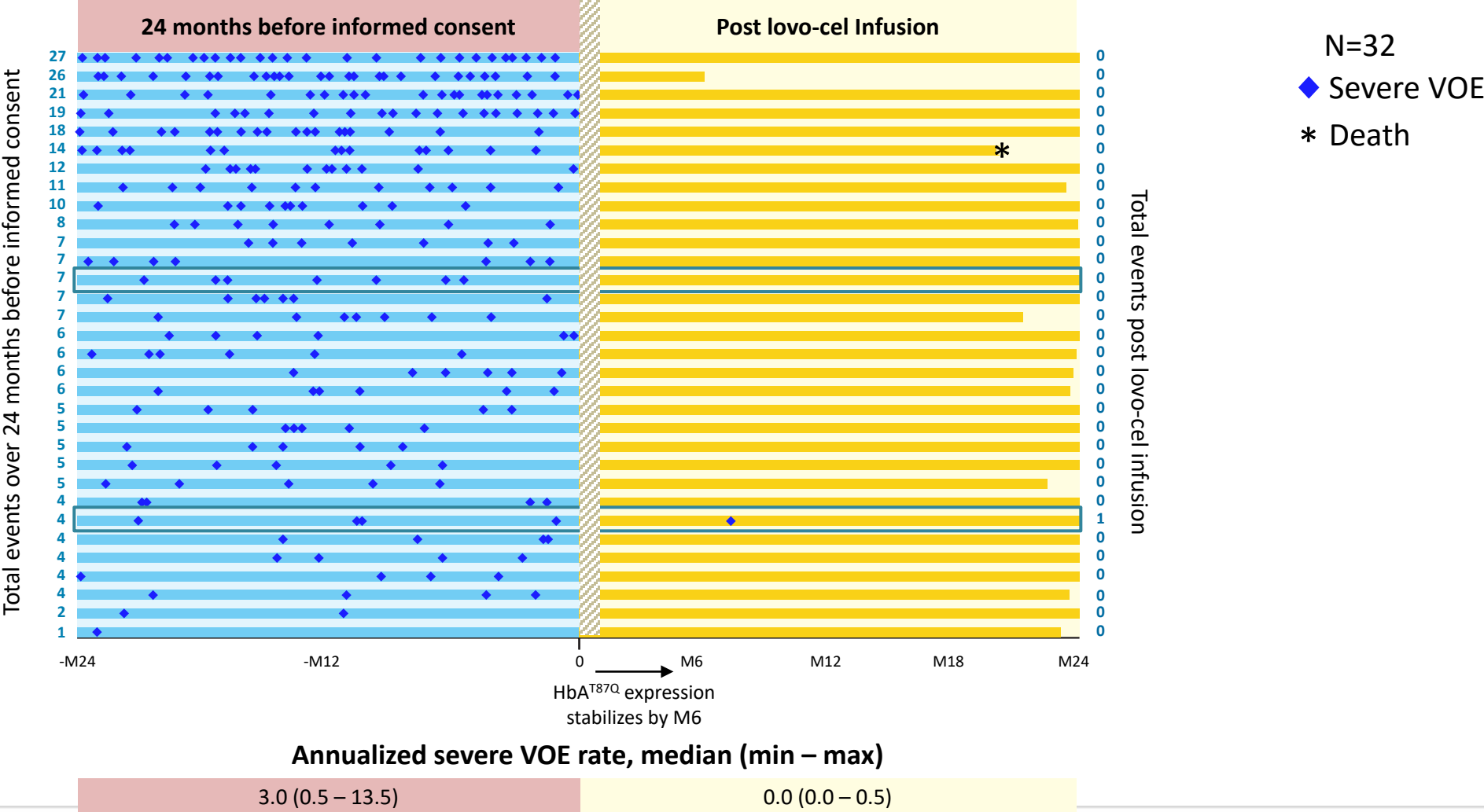
Serious treatment-emergent AEs <i>Reported in ≥2 patients</i>	N=36 <i>n (%)</i>
Pain	4 (11.1)
Abdominal pain	2 (5.6)
Anemia	2 (5.6)
Drug withdrawal syndrome	2 (5.6)
Nausea	2 (5.6)
Suicidal ideation	2 (5.6)
Vomiting	2 (5.6)

Grade ≥3 treatment-emergent AEs <i>Reported in ≥3 patients</i>	N=36 <i>n (%)</i>
Stomatitis	25 (69.4)
Thrombocytopenia	24 (66.7)
Neutropenia	20 (55.6)
Febrile neutropenia	15 (41.7)
Anemia	14 (38.9)
Leukopenia	12 (33.3)
Increased AST	6 (16.7)
Increased GGT	5 (13.9)
Nausea	4 (11.1)
Increased ALT	4 (11.1)
Decreased appetite	4 (11.1)
Pain	3 (8.3)

- No cases of veno-occlusive liver disease
- No cases of graft failure or vector-mediated RCL
- No insertional oncogenesis seen in any lovo-cel treated patient to date
- As previously reported, patient with significant baseline SCD-related cardiopulmonary disease died >18 months post-infusion (considered unlikely to be related to lovo-cel)
- **Two patients had persistent anemia, erythroid dysplasia and low-level trisomy 8 in the bone marrow, prompting further investigation**

AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; RCL, replication competent lentivirus; SCD, sickle cell disease.

Lovo-Cel (HGB-206 Group C) demonstrates no severe VOs pre and post infusion



Protocol severe VOs are shown.

Evaluation of the two patients with persistent anemia does not show emerging MDS diagnosis

Diagnostic and clinical features of MDS



Clonality



Driver mutations consistent with MDS



Clinical symptoms



Changes to blood counts



Dysplasia >10%

Adult patient

No clonal process identified
(vector related or otherwise)

No mutations or aneuploidy identified by
NGS, SNP microarray or karyotype
FISH results normal after M6

Patient is now transfusion dependent
and experiencing intermittent
exacerbations of chronic pain

No cytopenia aside from transfusion
dependent anemia

Dysplasia is consistent with stress
dyserythropoiesis

Pediatric patient

No clonal process identified
(vector related or otherwise)

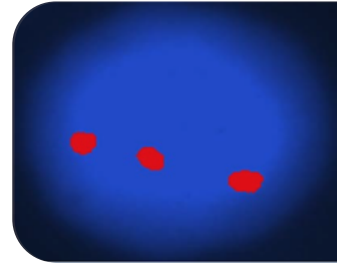
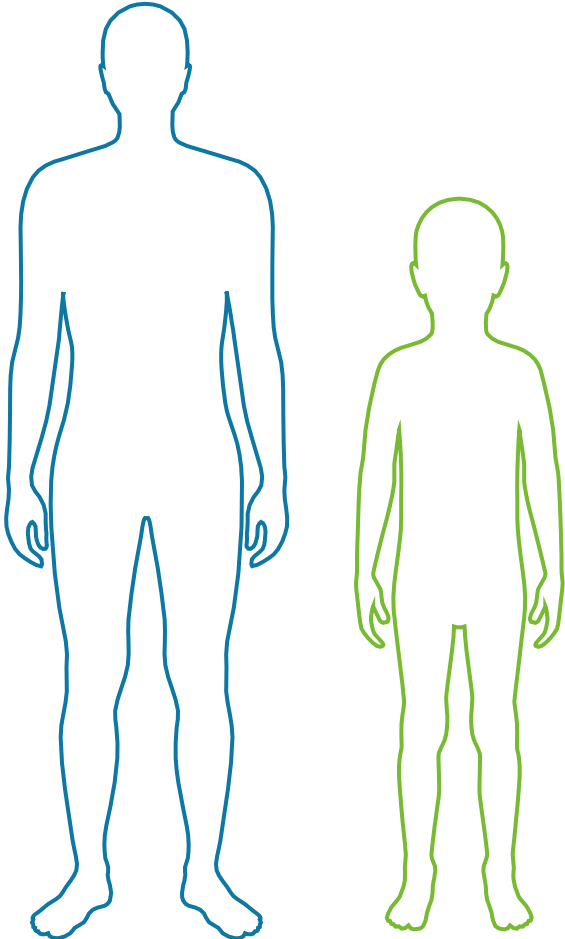
No mutations or aneuploidy identified by
NGS, WES, or karyotype
Low level trisomy 8 and 17 in BM only via FISH

Patient is clinically well and has had no
VOEs post-transplant

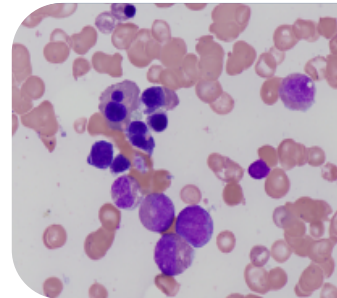
Neutropenia resolved
Untransfused hemoglobin was 9.7 g/dL at M24

Dysplasia is consistent with stress
dyserythropoiesis

Working diagnosis: α -thalassemia trait exacerbated by treatment with lovo-cel, likely driver of constellation of laboratory findings (globin chain imbalance)
 ≥ 2 α -globin gene deletions added as exclusion criteria clinical and laboratory findings



No evidence of clonal process; not consistent with emerging hematologic malignancy



Erythroid restricted dysplasia in bone marrow consistent with hemoglobinopathy



Anemia likely related to α : β -globin chain imbalance possibly exacerbated by treatment with lovo-cel

Conclusions from gene therapy presentations ASH 2022

- Gene therapy for sickle cell disease has the potential to be TRANSFORMATIVE
- **Gene therapy for sickle cell disease is generally well tolerated with most complications consistent with busulfan myeloablative conditioning**
- Patients with alpha-thalassemia trait (with two deletions) may be at increased risk of globin chain imbalance and persistent anemia

