POST-SAN DIEGO 2024
Novità dal Meeting della Società Americana di Ematologia

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Bologna
Palazzo Re Enzo
13-15 Febbraio 2025

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Sickle Cell Disease

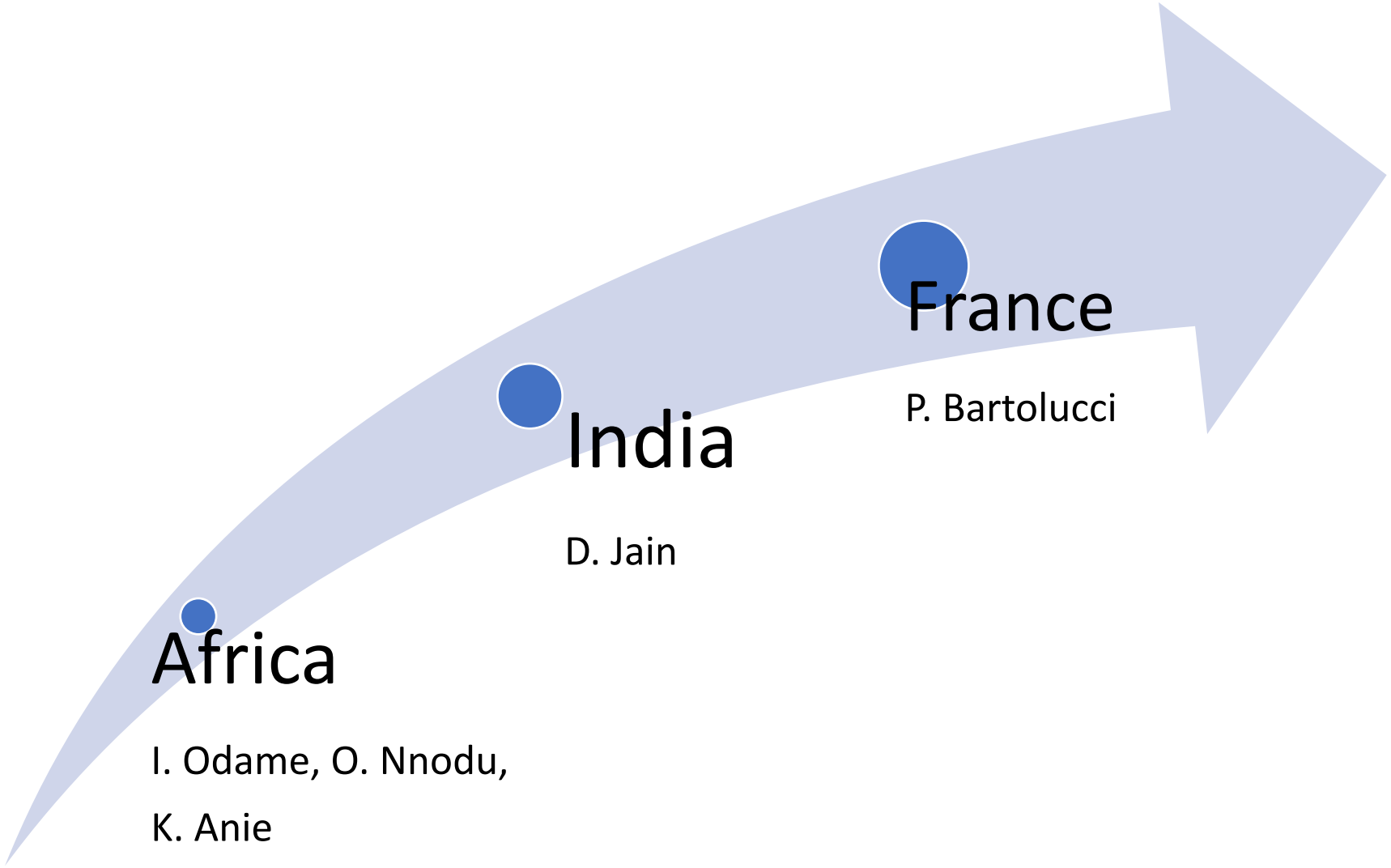
Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis						X	
Vertex						X	
Forma						x	
Novonordik					x		
Theravia					x	x	

Agenda

- Presentation of 3 managements of SCD
- Educational sessions
- Significant abstracts

Presentations on the management of SCD in different settings

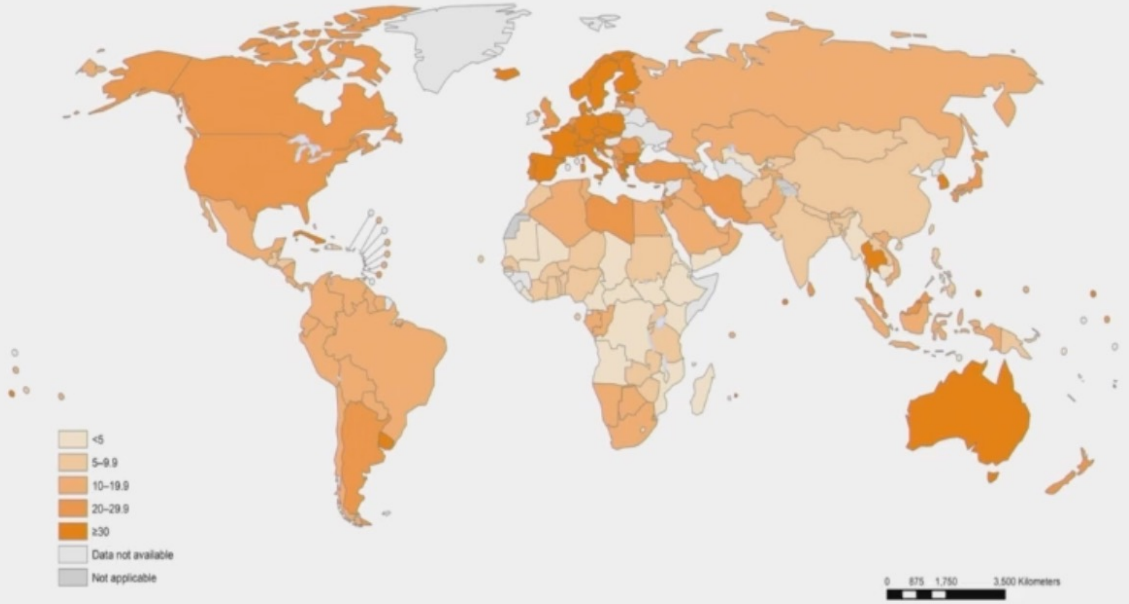


Causes of SCD-related mortality in sub-Saharan Africa

- Acute severe anemia
  - Malaria
  - Splenic sequestration
- Infections
  - Pneumonia
  - Sepsis
- Acute chest syndrome
- Multiple organ failure

Makani J et al. Blood 2010;115:215-220
McAuley et al. Blood 2010;116:1663-1668

Whole blood donations per 1000 population, 2018

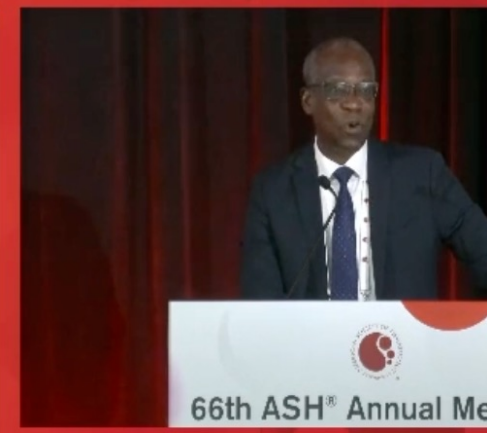


The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Blood and other products of human origin
World Health Organization

World Health Organization

WHO estimates that 10 donations per 1000 population are needed to meet blood transfusion requirements



Isaac odame

The lack of blood donations is one of the main causes of death in SCD patients in sub-Saharan Africa

Disease Modifying Treatments for SCA in Africa: Conclusions

- Hydroxyurea therapy is the most feasible disease modifying treatment for SCA in Africa

- Universal access to quality-assured HU (available + affordable)
  - Systematic education/training of health professional using WHO guidelines
  - Promote patient/family awareness of HU benefits
  - Global funding and partnerships
    - WHO and UNICEF
    - Africa CDC and African Medicines Agency
      - Promote local manufacture of quality assured HU
    - Clinton Health Access Initiative
    - World Coalition on SCD
    - Public-private partnerships with high government commitment
    - International donor agencies

Today, non -integration of pilot programs into national public health services

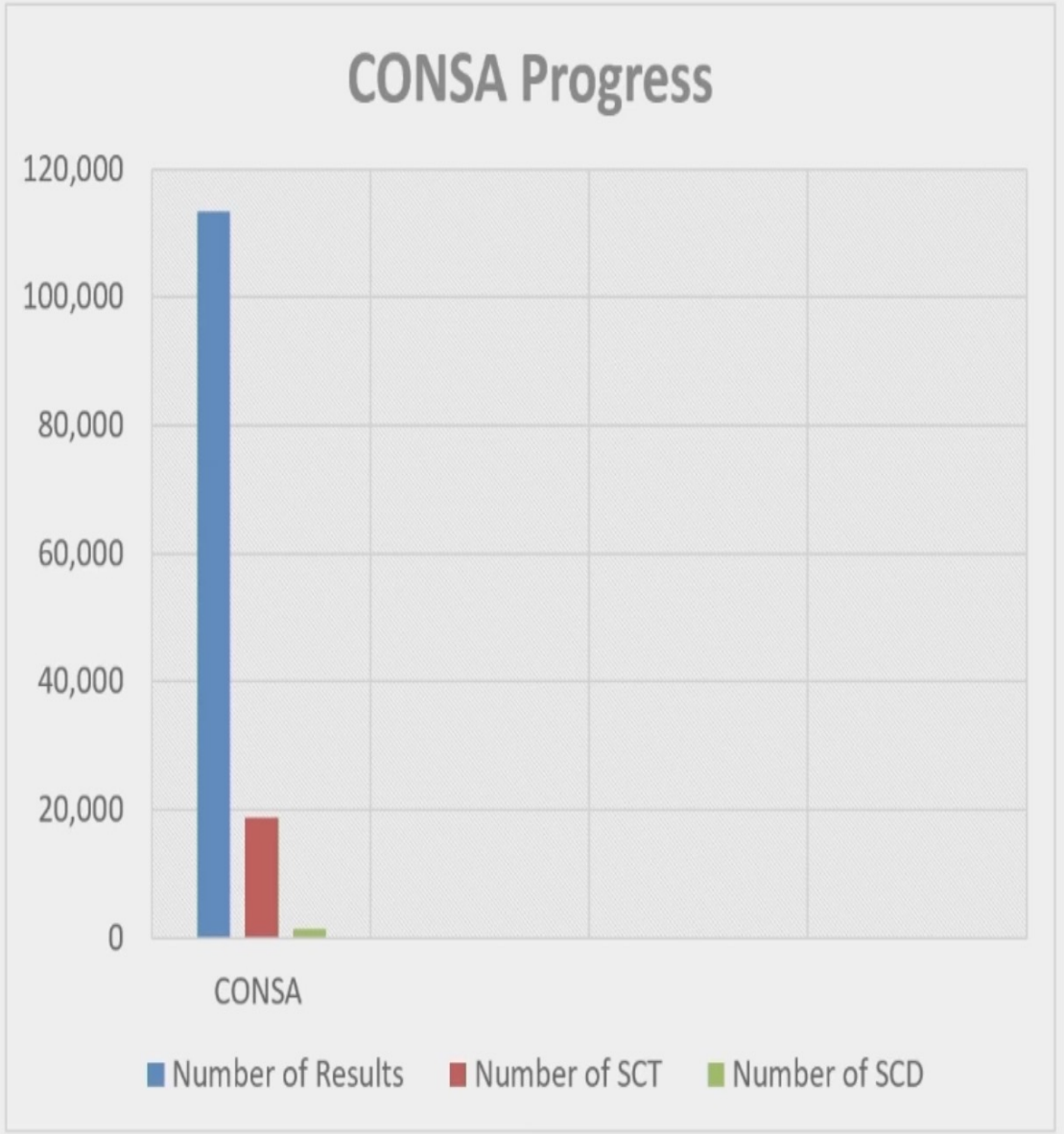
Initiatives to Enhance NBS -I Consortium on Newborn Screening in Africa (CONSA)

CONSA aims to demonstrate the feasibility of NBS and early therapeutic interventions for babies with SCD in sub-Saharan Africa

O Nnodu

CONSA progress

Screening Results
- Number of Results: 113,418
- Number SCT: 18,875 (16.6%)
- Number SCD: **1,520 (1.3%)**
- **Follow Up**
- First Clinical Visit: 630 (42%)



Denial of positive test results by parents because of apparently healthy babies within the first six months and stigma

Beginning of a new era
First (Pediatric) Sickle Cell Clinic, Nagpur 1983

- children with SCD crying with pain
- Sickle slide test and paper electrophoresis

Limited Tools!

Oral Rehydration

Folic Acid

Sahli's Hemoglobinometer

Initiation of Hydroxyurea in India in year 2000

Establishing Low-Dose HU as Standard of Care

Global

European Journal of Haematology 2023

HU MTD versus fixed low-dose in adults with SCD

Low-dose HU may offer similar benefit as MTD for SCD in LMICS

Low dose HU- the solution to the global SCD?

HU Studies in India

Blood Cells, Molecules, and Diseases

HU in SCD clinic-Pharm efficacy Italia, Jain *et al 2009*

Indian Pediatrics

Efficacy of Fixed Low Dose HU Jain *et al 2012*

HEMOGLOBIN

Low Dose HU Efficacy in reducing crises and transfusion inSCD
D Patel *et al 2014*

The Journey from Early Beginnings to Comprehensive Care, Community Advocacy, Political Will, Screening and Research

1952

Leshman Catbush

Solanki et al

1956

1985

Sickle Cell Clinic

– Penicillin
– Cellulose acetate

1992

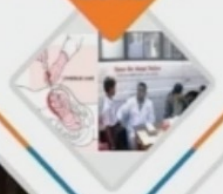
1998

Tribal experience
(JAY VIGYAN PROJECT, ICMR)
Solubility test
Recognition of severe sickle phenotype in spite of high HbF %.

– NBS *Targeted*
– Hydroxyurea - *Low fixed dose*

2000

2002



– Prenatal Diagnosis
– Comprehensive Healthcare Programme

Prenatal Diagnosis

2004 2005

2016

Documentation/ publication on indian sickle cell Disease

Curative Therapies HSCT for sickle cell Disease

2018

2022

IGIB
Gene Therapy CSIR

– Yoga.
– Complication of SCD stroke, Renal disease, Avascular necrosis of bone, Acute chest syndrome, **Hypersplinism**, etc. recognised

National Sickle Cell Anaemia Elimination Mission

Launched the (NSCAE)

2023

2024

Implementation in 17 states of (NSCAE)

Political will and well-funded governmental priority to transform sickle cell care.

– Clinical trials (low dose verses escalation dose of **HU – Liquid HU formulation**, Crizanlizumab, L-Glutamine and voxelotor, alternative medicine).
– Rapid progress in gene therapies
– Awareness
– Screening 0 to 40 years.
– Management of affected individuals

Screening for SCD | **Prenatal Diagnosis** | **Hydroxyurea** | **Newborns** | **Comprehensive Health Care**

National Mission for Elimination of Sickle Cell Disease as a Public Health Burden - 2023

स्वास्थ्य एवं परिवार कल्याण मंत्रालय
MINISTRY OF HEALTH AND FAMILY WELFARE

NATIONAL HEALTH MISSION

NATIONAL SICKLE CELL ANAEMIA ELIMINATION MISSION

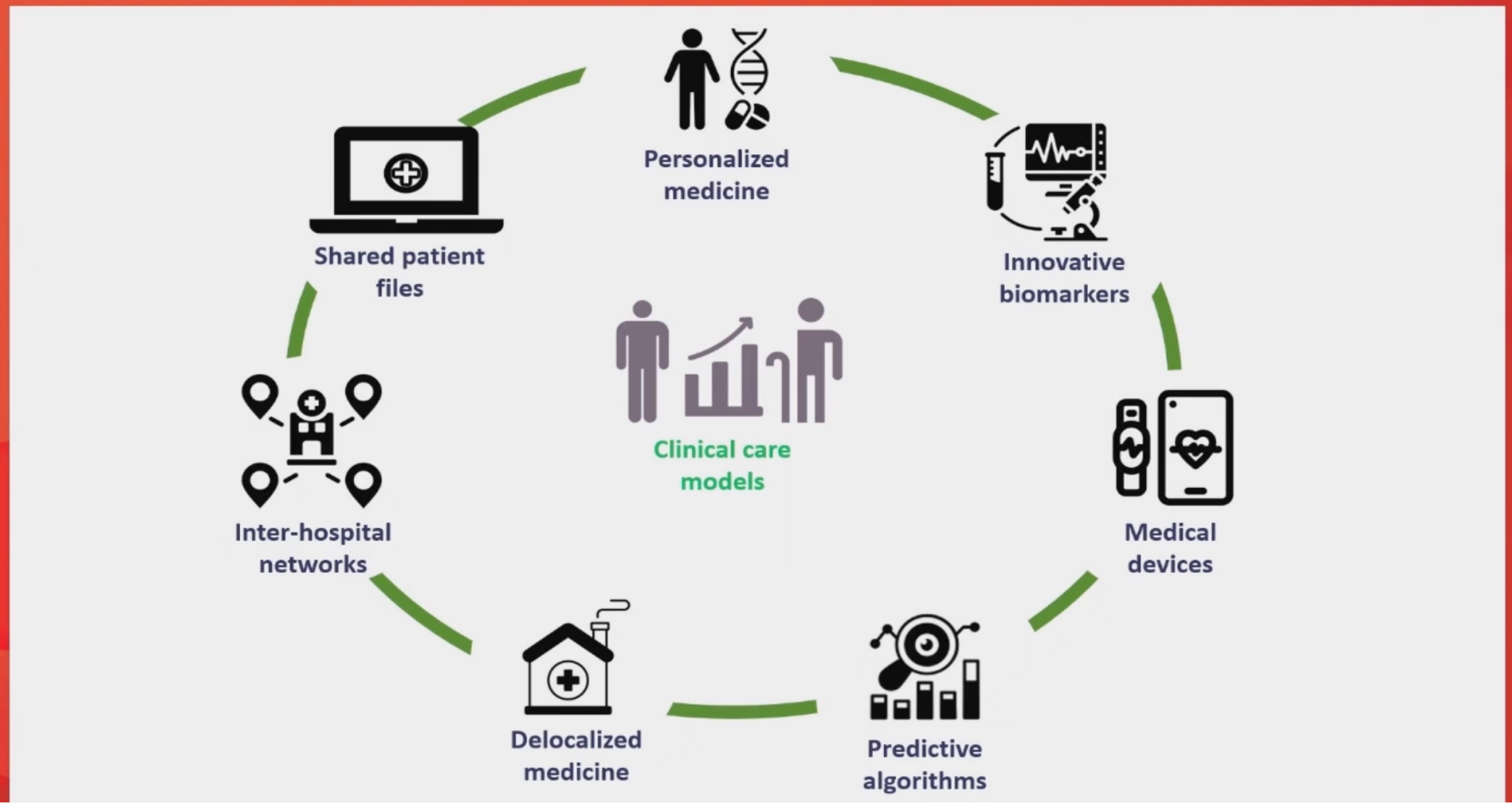
जनजातीय कार्य मंत्रालय
MINISTRY OF TRIBAL AFFAIRS

National Sickle Cell Anaemia Elimination Mission

About Mission

Sickle cell disease is a genetic blood disease which affects the whole life of affected patient. It is more common in the tribal population of India, but occurs in non tribals too. It not only causes anemia but also pain crises, reduced growth, and affects many organs like lungs, heart, kidney, eyes, bones and the brain. India has the largest density of tribal population, globally. As per Census 2011, India has an 8.6% tribal population which is 67.8 million across the Indian states. The MoHFW tribal health expert committee report has listed sickle cell disease as one of the 10 special problems in tribal heath that affect the tribal people disproportionately, thus making this an important intervention. Ministry of health under NHM initiated the work on hemoglobinopathies (Thalassemia & Sickle Cell Disease) in 2016 wherein comprehensive guidelines on prevention and management of heamoglobinopathies were released and provision of funds towards screening and management of Sickle cell disease were made. Thereafter, as per the State's proposals, support is continuously being provided. However, the pandemic reduced the efforts towards prevention through screening and IEC activities. Now, it is felt that a separate scheme/Mission to detect, management, prevention and awareness needs to be initiated.

In France,
Institutional funding of a national network, the « Filière »,
enabling exchanges between centres of expertise
Ambition of patient-centred and delocalized medicine



Pablo Bartolucci

The French National Network, la Filière

PNDS
French Guidelines

Research tools

Workgroups

- Care pathway
- Data base
- Transfusion
- Medical imaging
- Multidisciplinary coordination
- Teaching and information
- Research
- Patients associations
- Therapeutic education
- Transition
- Psycho social

MCGRE

FILIÈRE SANTÉ MALADIES RARES

website

Plenary sessions

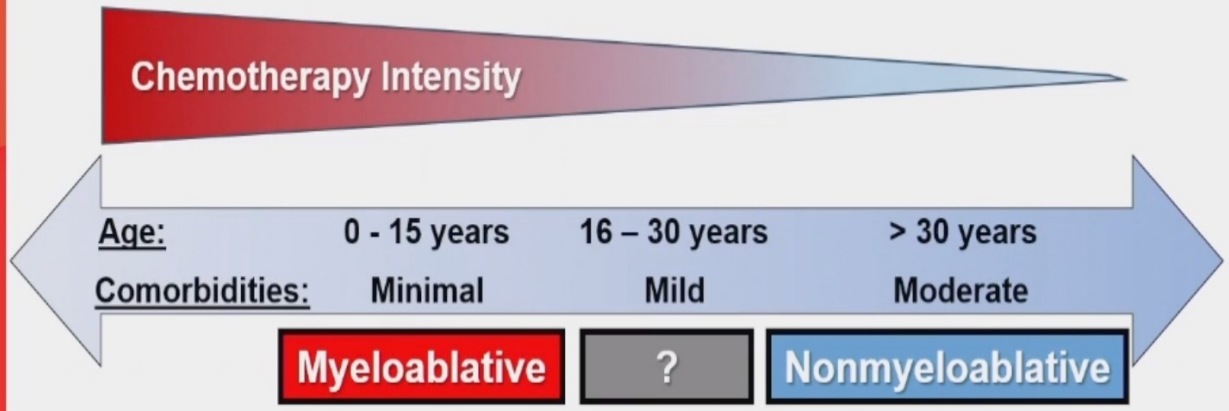
Multidisciplinary meetings

HSCT & SCD: HLA-MATCHED

In 2 separate groups of patients treated with myeloablative conditioning regimens[1,2]

- **Age > 15 years**: ↑ GVHD risk 4.4-fold
- **Age > 10 years**: ↑ Mortality 21-fold, Graft failure 1.6-fold, Chronic GVHD 1.9-fold

1. Bernaudin F et al, Haematologica 2020;
2. Arnold SD et al. Haematologica 2017



Busulfan-based

- ↑ Stable engraftment (90 - 95%)
- ↑ Infertility, GVHD (10 – 20%)

Eapen M et al. Lancet Haematol 2019

Alemtuzumab/TBI + Sirolimus

- ↓ GVHD (0 – 2%), Preserved fertility
- ↑ Graft failure (15%), MDS/AML (2%)

Alzahrani et al. Br J Haematol 2020

NMA in SCD Adults:

200 patients; Riyadh, Saudi Arabia[3]

- 88% stable engraftment
  - 76% off sirolimus
- No clonal evolution or MDS/AML
- 26 pregnancies, 20 births

20 patients, + Azathioprine/HU[4]

- 5% graft failure & 0% cGVHD

3. Damlaj M et al, Am J Hematol 2024
4. Dovern E et al. Am J Hematol 2024

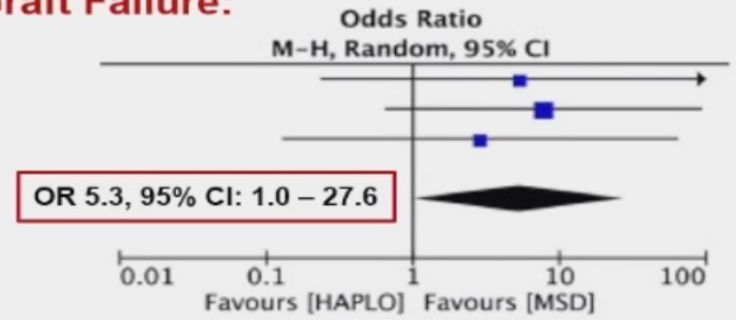
UI Health | UIC

Santosh Saraf

HSCT & SCD: HAPLO-MATCHED

Meta-Analysis (n = 179)

Graft Failure:



Outcomes	Pooled % (95% CI)
Acute GVHD (Gr ≥2)	4% (2 – 12%)
Chronic GVHD	11% (7 – 16%)
Stable Engraftment	93% (80 – 98%)
Overall Survival	91% (85 – 94%)

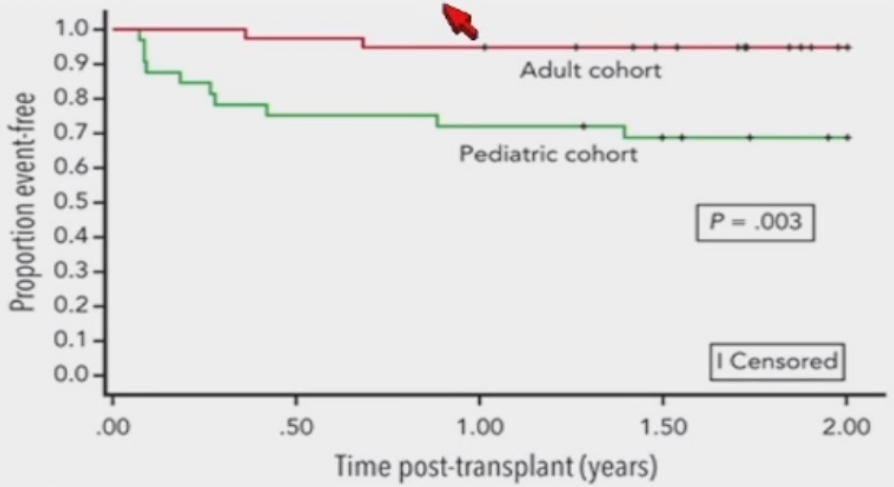
Aydin M et al. *Transplant & Cell Therapy* 2021

Phase 2, Multicenter Trial

+ Thiotepa to Johns Hopkins haplo regimen

- 70 patients included in analysis, median age 19 (IQR, 14 – 25) years

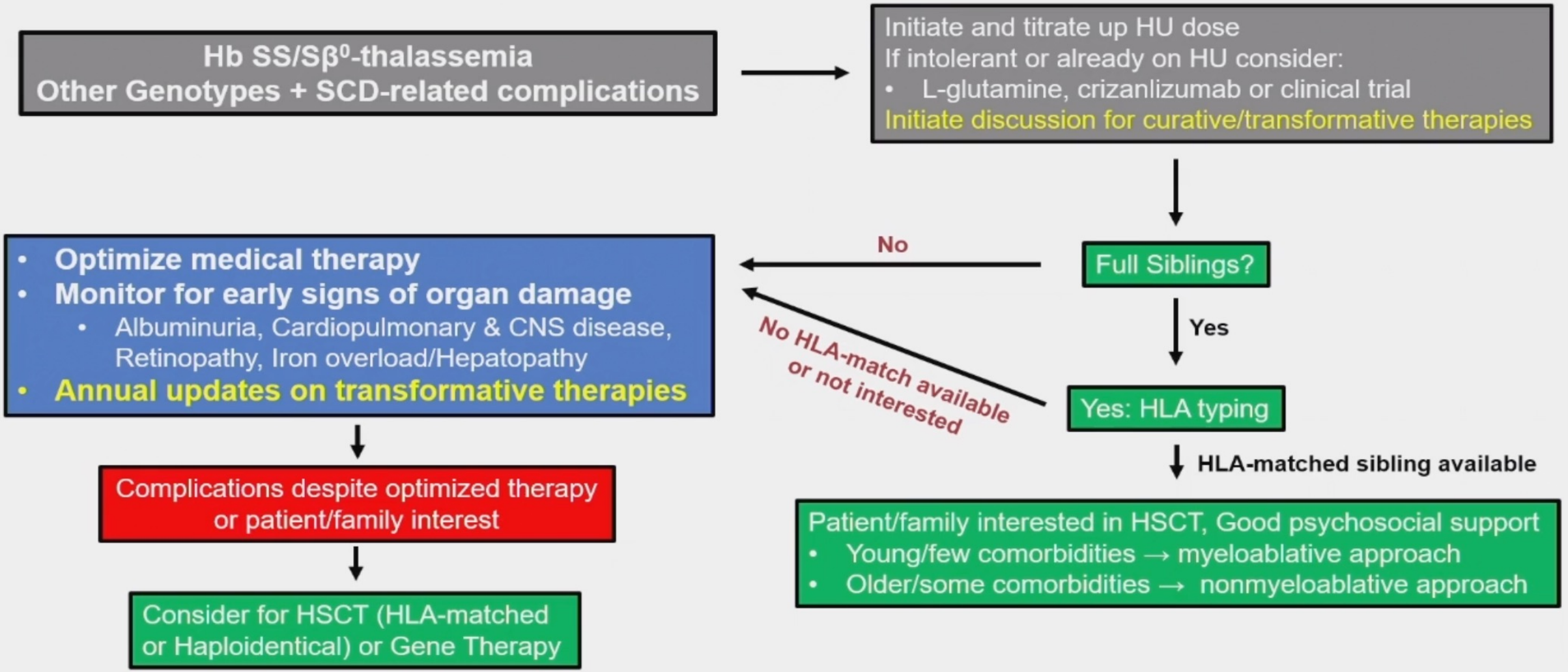
Infection-related mortality: **7%**
Moderate-severe cGVHD: **10%**; 19% children, 3% adults
Event-free survival: **89%;** 68% children, 95% adults
2-Yr overall survival: **94%;** 94% children, 95% adults



Kassim A et al. *Blood* 2024

UI Health | UIC

My Approach for patients with SCD



Gene Therapy for Sickle Cell Disease

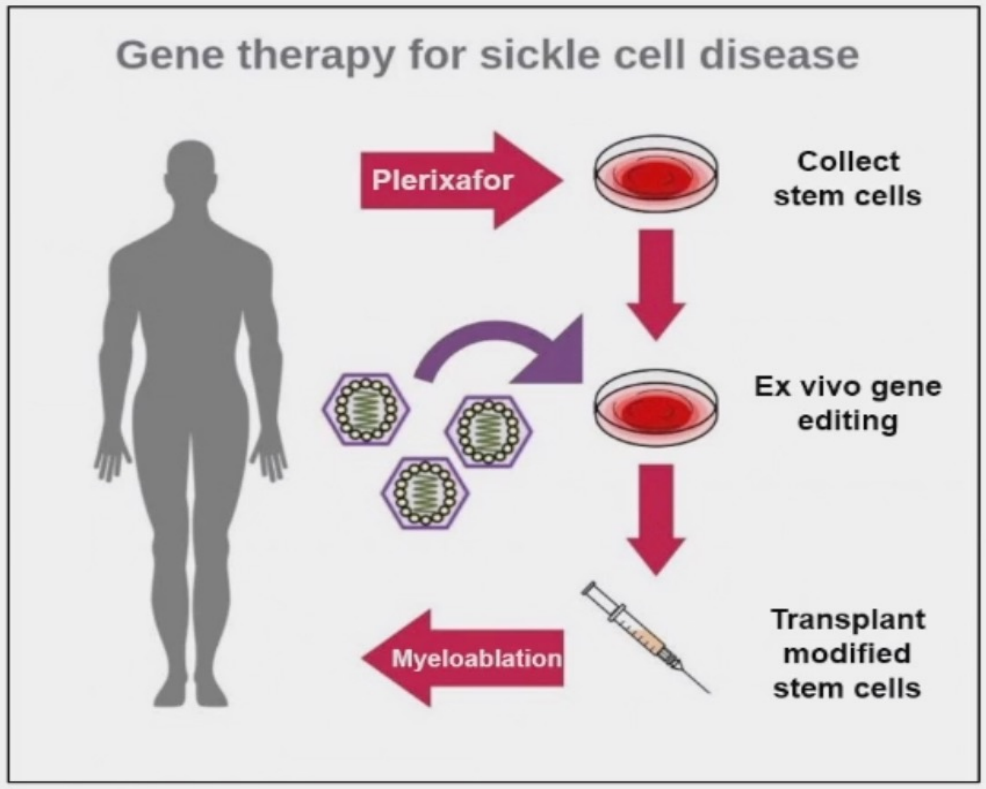


Figure adopted from NHLBI

	CRISPR-Cas9[1] Exagamglogene autotemcel (Exa-cel) N = 44	Lentivirus[2] Lovotibeglogene autotemcel (Lyfgenia) N = 35
Target	BCL11A	$\beta^{A\text{-}T87Q}$
Regimen	Myeloablative, PK-adjusted Busulfan	
Age (years)	21 ± 6	24 (12 – 38)
Hb SS Genotype	40 (91%)	35 (100%)
$CD34^+$ (10^6 cells/kg)	4.0 (2.9 – 14.4)	6.9 (3.0 – 25.0)
Follow up (months)	19 (1 – 48)	17 (4 – 38)
Key Differences:	VOC 2 – 10/year Stroke history excluded	VOC ≥ 4/year (no cap) 14% (5/35) stroke history Trisomy 8 in 2 with α-thal

1. Frangoul H et al. NEJM 2024; 2. Kanter J et al. NEJM 2022

Limitations By the Number

- ~100,00 patients in the US Population
- Barriers to Uptake: Capacity
- BMT Centers
  - 1,149 transplants for SCD from 2000 to 2017 from 94 centers - ~67 transplants/year
  - 1,718 transplants from 1991-2021 – ~86 transplants/year
- Activated Treatment Centers
  - 50 for lovotibeglogene autotemcel (Lyfgenia)
  - 33 for exagamglogene autotemcel (Casgevy)
  - Qualified & Authorized treatment centers 5-6/year, Large centers may be able to treat up to 10 patients/year for gene therapy

Data and Statistics on Sickle Cell Disease | Sickle Cell Disease (SCD) | CDC, Qualified Treatment Center Locator, Authorized Treatment Center Locator | , St Martin A, Hebert KM et al. Long-term Survival after Hematopoietic Cell Transplant for Sickle Cell Disease Compared to the United States Population. Transplant Cell Ther. 2022 Jun;28(6):325, **Lakshmanan Krishnamurti,Jingchen Liang,Zili He,Yanhong Deng,Vineetha R. Nallagatla,Rohaum Hamidi,Aron Flagg,Niketa Shah, Incidence and risk factors of pain crisis after hematopoietic cell transplantation for sickle cell disease, Blood Adv, 2024,**

Payal Desai

An Update on Lovotibeglogene Autotemcel (Lovo-cel) Clinical Trials for Sickle Cell Disease (SCD) and Analysis of Early Predictors of Response to Lovo-cel

Stacey Rifkin-Zenenberg,[1*] Julie Kanter,[2] Melissa A. Kinney,[3] Janet L. Kwiatkowski,[4,5] Robert S. Nickel,[6] Mark C. Walters,[7] Suhag Parikh,[8] Alexis A. Thompson,[4,5] Anil P. George,[9] Markus Y. Mapara,[10] Paul L. Martin,[11] Anjulika Chawla,[3] Ankit Lodaya,[3] Lin Pan,[3] Emily Sheldon-Waniga,[3**] Francis J. Pierciey Jr,[3] John F. Tisdale,[12] Ashish O. Gupta[13]

[1]Hackensack University Medical Center, Hackensack, NJ; [2]Univerity of Alabama at Birmingham, Birmingham, AL; [3]bluebird bio, Inc., Somerville, MA; [4]Children's Hospital of Philadelphia, Philadelphia, PA; [5]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [6]Children's National Hospital, Washington, DC; [7]University of California San Francisco Benioff Children's Hospital, Oakland, CA; [8]Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Emory University, Atlanta, GA; [9]Baylor College of Medicine, Houston, TX; [10]Columbia Center for Translational Immunology, Columbia University Irving Medical Center, New York, NY; [11]Duke University, Durham, NC; [12]National Heart, Lung, and Blood Institute and National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD; [13]University of Minnesota, Minneapolis, MN, USA

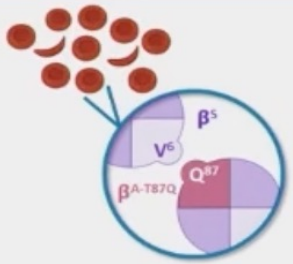
*Presenting author. **Former employee of bluebird bio, Inc.*

This presentation includes off-label information

66th ASH Annual Meeting and Exposition; December 7-10, 2024 - Abstract #511

S. Rifkin-Zenenberg

Lovo-cel for the Treatment of SCD Using the Refined Manufacturing Process (HGB-206 Group C and HGB-210)



Lovo-cel consists of genetically modified autologous stem and progenitor cells to produce RBCs containing HbA^{T87Q}, which due to a single amino acid change, has anti-sickling properties and normal adult HbA oxygen affinity[1-3]

Initiated mobilization
N=71
[HGB-206 Group C: 43; HGB-210: 28]

Transplant population
n=58
[HGB-206 Group C: 36; HGB-210: 22]

Evaluable for efficacy
Globin response evaluable[a]: n=50
VOE evaluable[b]: n=38

Pending lovo-cel infusion
n=5
[HGB-210: 5]

Discontinued prior to infusion
n=8
[HGB-206 Group C: 7; HGB-210: 1]
Failed to mobilize (n=1)
Physician decision (n=2)
Participant withdrawal (n=5)

Recently infused
n=16
(not evaluable for VOE-CR at data cutoff)

Follow-up time

Among 58 participants who received lovo-cel:

- Median follow-up time: **47.7** months (4.0 years)
- Overall exposure: **195.6** participant-years
- Longest follow-up: **79.4** months (6.6 years)[c]

[a]Globin response–evaluable participants who achieved globin response or have ≥18 months of follow-up. [b]Participants who had ≥1 adjudicated VOE between 6 and 18 months post drug product infusion or have ≥18 months of follow-up. Includes participants with ≥4 VOEs at baseline. [c]These data refer to the longest follow-up in participants treated with the current manufacturing process.

Hb, hemoglobin; HbA, adult Hb; HbA^{T87Q}, anti-sickling Hb; RBC, red blood cell; SCD, sickle cell disease; VOE, vaso-occlusive event; VOE-CR, complete resolution of VOEs.

1. Magrin E, et al. *Nat Med.* 2022;28(1):81-88. 2. Pawliuk R, et al. *Science.* 2001;294(5550):2368-2371. 3. Kanter J, et al. *N Engl J Med.* 2022;386(7):617-628.

Demographics and Clinical Characteristics: Transplant Population (HGB-206 Group C and HGB-210)

Demographics and participant characteristics	Total N=58
Age at enrollment, median (min, max), years	21 (8, 38)
≥18 years, n (%)	42 (72.4)
<18 years, n (%)	16 (27.6)
Sex, n (%)	
Male	35 (60.3)
Follow-up post infusion, median (min, max), months	47.7 (1.2, 79.4)
Genotype for β-globin, n (%)	
β^S/β^S	55 (94.8)
β^S/β^0	3 (5.2)
Genotype for α-globin, n (%)	
αα/αα	41 (70.7)
αα/-$\alpha^{3.7}$	15 (25.9)
-$\alpha^{3.7}$/-$\alpha^{3.7}$	2 (3.4)
Baseline clinical characteristics	
Annualized number of adjudicated VOEs,[a,b,c] median (min, max)	3.5 (1.5, 16.5)[d]
Annualized number of adjudicated sVOEs,[a,b,c] median (min, max)	3.3 (0.5, 13.0)[d]
Annualized number of pRBC transfusions,[a] median (min, max)	3.8 (0, 17.0)[e]
Total Hb, median (min, max),[f] g/dL	8.7 (6.1, 12.5)
Prior hydroxyurea use, n (%)	51 (87.9)

Characteristic Median (min, max)	Total N=58
Mobilization and engraftment	
No. of mobilization cycles	2.0 (1, 4)
Time to neutrophil engraftment,[g,h] days	20.0 (12, 35)
Time to platelet engraftment,[h,i] days	36.0 (19, 157)
Duration of hospitalization,[j] days	36.0 (26, 65)
Drug product characteristics	
Total CD34+ cell dose, ×10^6 cells/kg	6.6 (3.0, 13.3)
VCN, copies/diploid genome	4.1 (2.3, 6.8)
%LVV+ cells	83.0 (63, 93)

- Demographics and treatment/drug product characteristics are consistent with previous reports
- 83% of participants required only 1 or 2 mobilization cycles

[a]In the 24 months prior to consent. [b]Transplant-VOE population. [c]As confirmed by the Independent Event Adjudication Committee after participant enrollment. [d]n=38. [e]n=42. [f]Baseline total Hb is defined as the average of 2 most recent qualifying Hb assessments made prior to or during screening that met the following criteria: assessments were separated by ≥1 month, assessments were drawn no earlier than 24 months prior to informed consent and could include the Hb result from screening, and the participant did not receive a pRBC transfusion within 3 months prior to each Hb assessment. [g]Neutrophil engraftment was defined as achieving 3 consecutive laboratory values of ≥0.5×10^9 cells/L (after initial postinfusion nadir) obtained on different days by day 43 post infusion; time to neutrophil engraftment was measured from infusion (day 1) to the first day of the 3 consecutive measurements. [h]Following data cutoff, all participants achieved neutrophil and platelet engraftment. [i]Platelet engraftment was defined as achieving 3 consecutive laboratory values of ≥50×10^9 cells/L (after initial postinfusion nadir) obtained on different days without receiving any platelet transfusions for 7 days immediately preceding and during the evaluation period; time to platelet engraftment was measured from infusion (day 1) to the first day of the 3 consecutive measurements. [j]Duration of hospitalization from conditioning to discharge.

Hb, hemoglobin; LVV, lentiviral vector; pRBC, packed red blood cell; sVOE, severe VOE; VCN, vector copy number; VOE, vaso-occlusive event.

Summary of Safety From Day 1 Through Last Follow-Up: Transplant Population (HGB-206 Group C and HGB-210)

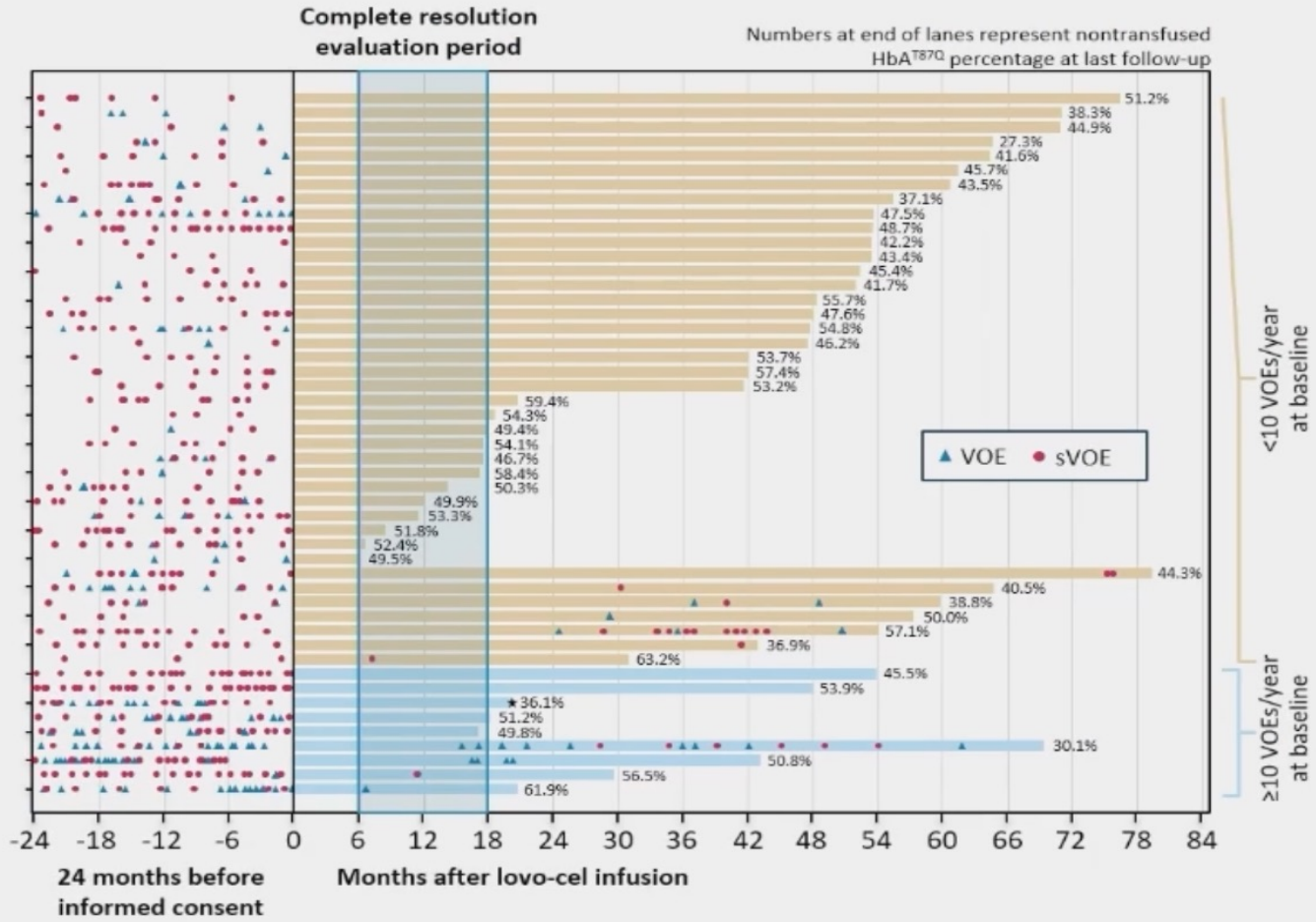
	Total N=58
TEAEs, n (%)	
Any grade	58 (100)
Grade ≥3	56 (96.6)
Lovo-cel–related AEs,[a] n (%)	**4 (6.9)**
Anemia[b,c]	2 (3.4)
Abdominal discomfort	1 (1.7)
Blood pressure diastolic decreased	1 (1.7)
Myelodysplastic syndrome[b,c]	1 (1.7)
Nasal congestion	1 (1.7)
Participants with any serious TEAE, n (%)	**48 (82.8)**
Participants with lovo-cel–related serious AEs[a]	2 (3.4)

- Consistent with previous reports, the lovo-cel treatment regimen safety profile reflects the known effects of underlying SCD and myeloablative conditioning
- A majority of TEAEs occurred within 1 year post lovo-cel infusion and were known consequences of conditioning with busulfan
- The previously reported diagnosis of MDS at month 30 is still under investigation as of month 48. CBC is stable, and the participant is clinically well and has not required any treatment for MDS
- There was 1 case of grade 3 veno-occlusive disease of the liver in the HGB-210 study that resolved
- There were no cases of graft failure or GVHD
- There were no vector-related complications and no insertional oncogenesis or clinically significant oligoclonality

[a]Sponsor assessed. [b]Serious AE. [c]Two participants had β^S/β^S and α-thalassemia trait ($-\alpha^{3.7}/-\alpha^{3.7}$). One was diagnosed with MDS by the principal investigator based on findings of cytopenia, dysplasia, and karyotype.

AE, adverse event; CBC, complete blood count; GVHD, graft-versus-host disease; MDS, myelodysplastic syndrome; SCD, sickle cell disease; TEAE, treatment-emergent adverse event.

86.8% (33/38) of Participants Achieved Complete Resolution of All VOEs (Primary Endpoint, 6-18 Months)



VOE-CR[a]	sVOE-CR[a]
86.8% (33/38)	94.7% (36/38)

- Duration VOE-free among participants who achieved VOE-CR: 42.4 (12.2, 70.5) months[b]
- **100%** (10/10) of pediatric participants (<18 years) achieved VOE-CR
- 11 participants had VOEs post infusion, 6 participants experienced VOEs after the 6- to 18-month assessment period
  - In the 11 participants who had VOEs post infusion, there was an average of 84% reduction in annualized VOEs (range, 46%-97%), with 7/11 participants having >90% reduction
- Four of the 5 participants who did not achieve VOE-CR had ≥10 annualized VOEs at baseline

★ Death, due to significant baseline SCD-related cardiopulmonary disease; not considered related to lovo-cel. An Independent Event Adjudication Committee confirmed VOEs met protocol criteria. Single VOEs for 2 participants shown here were retracted by the investigator post adjudication. [a]In the 6-18 months post infusion; participants with ≥18 months of follow-up and ≥4 VOEs ≤2 years pre-enrollment. [b]Median (min, max).

Hb, hemoglobin; HbA^{T87Q}, anti-sickling Hb; SCD, sickle cell disease; sVOE, severe VOE; sVOE-CR, complete resolution of sVOEs; VOE, vaso-occlusive event; VOE-CR, complete resolution of VOEs.

Population: Participants with ≥6 months of follow-up

Data as of July 2024

Conclusions

- One-time lovo-cel treatment results in durable biologic effect and clinical benefit
  - Sustained HbA^{T87Q} production
  - Elimination of VOEs and sVOEs in a majority of participants through last follow-up (median, 47.7 months)
    - 100% of pediatric participants achieved VOE-CR and sVOE-CR
    - 96.7% of participants with <10 annualized VOEs/year at baseline achieved VOE-CR and sVOE-CR
- The safety profile of the lovo-cel treatment regimen was consistent with underlying SCD and known effects of myeloablative conditioning
- Models developed in a post hoc analysis enable prediction of the likelihood of VOE-CR and sVOE-CR using measurements as early as 6 months post treatment
- In the 11 participants who had VOEs >6 months post drug product infusion, there was an average 84% reduction in annualized VOEs (range, 46%-97%), with 7/11 participants having >90% reduction
- Participants with ≥10 VOEs/year had durable clinical benefit, with 50% achieving VOE-CR. In addition, there was a marked reduction in annualized VOE events and VOE-related hospitalization days post lovo-cel
- Patients who experienced VOEs during long-term follow-up had other clinical factors that may have contributed to the pain event. Occurrence was independent of HbA^{T87Q} levels. Further investigation of the complex causes of pain during long-term follow-up is needed and ongoing
- Ongoing follow-up in HGB-210 and LTF-307 will continue to assess the safety and long-term impact of lovo-cel

HbA^{T87Q}, anti-sickling Hb; SCD, sickle cell disease; sVOE, severe VOE; sVOE-CR, complete resolution of sVOEs; VOE, vaso-occlusive event; VOE-CR, complete resolution of VOEs.

Durable Clinical Benefits with Exagamglogene Autotemcel for Transfusion-Dependent β-Thalassemia

Franco Locatelli

Franco Locatelli,[1] Peter Lang,[2] Roland Meisel,[3] Donna Wall,[4] Selim Corbacioglu,[5] Amanda M. Li,[6] Josu de la Fuente,[7] Ami J. Shah,[8] Ben Carpenter,[9] Janet L. Kwiatkowski,[10] Markus Mapara,[11] Robert I. Liem,[12] Maria Domenica Cappellini,[13] Mattia Algeri,[14] Antonis Kattamis,[15] Sujit Sheth,[16] Stephan Grupp,[10] Hayley Merkeley,[17] Kevin H.M. Kuo,[18] Joachim Rupprecht,[2] Puja Kohli,[19] Gang Xu,[19] Leorah Ross,[19] Yael Bobruff,[19] Bo Tong,[19] William Hobbs,[19] Haydar Frangoul[20]

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TDT: Key Demographic Characteristics and Treatment Features

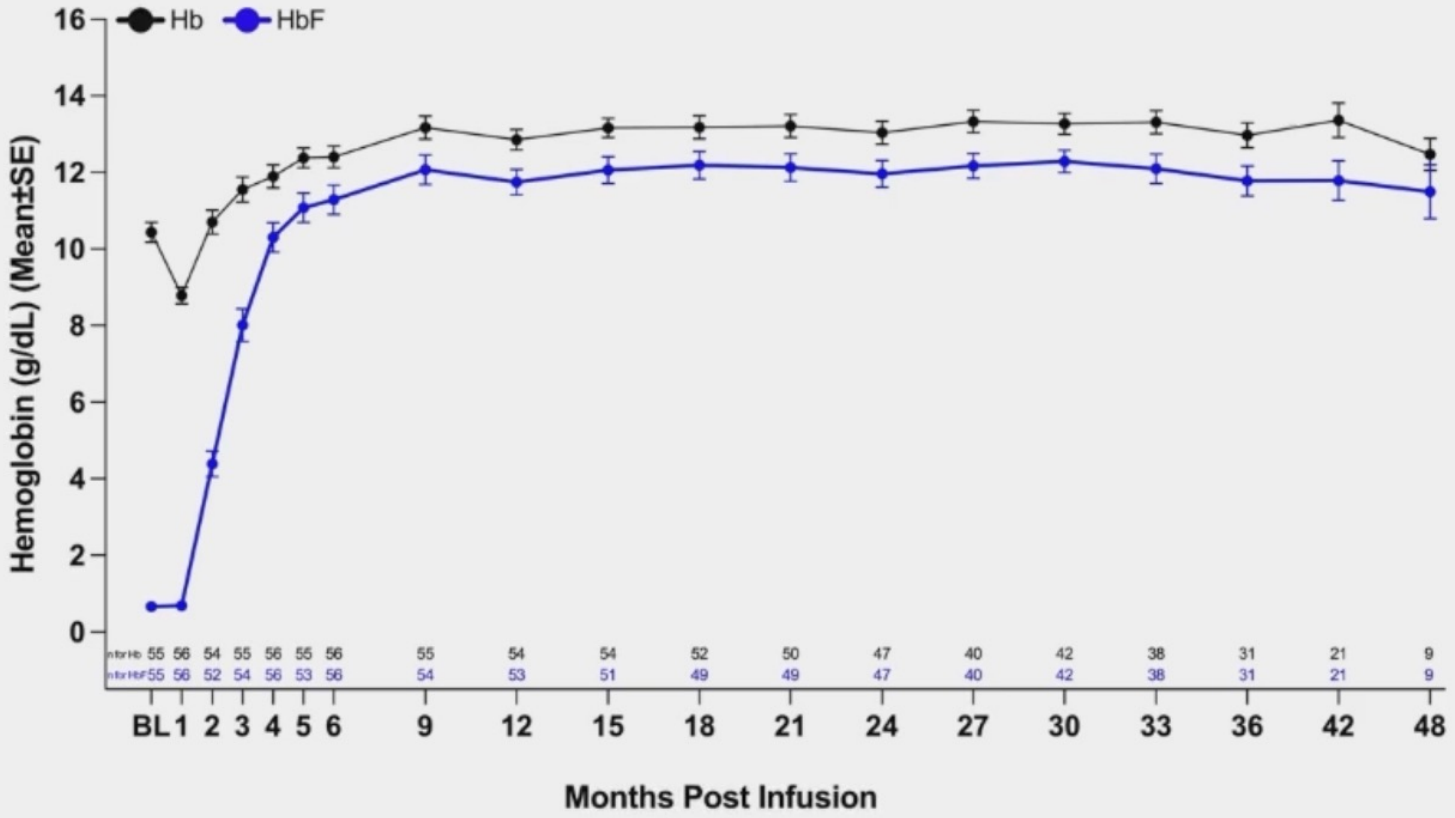
	Full Analysis Set[a] N = 56	Primary Efficacy Set[b] N = 54
Age (years) at screening, mean (SD)	21.2 (6.5)	21.3 (6.6)
≥12 and <18 years, n (%)	20 (35.7)	19 (35.2)
≥18 and ≤35 years, n (%)	36 (64.3)	35 (64.8)
Genotype, n (%)		
β^0/β^0	22 (39.3)	21 (38.9)
β^0/β^0-like (β^0/IVS-I-110; IVS-I-110/IVS-I-110)	13 (23.2)	12 (22.2)
Non-β^0/β^0-like	21 (37.5)	21 (38.9)
Neutrophil Engraftment (days)[c]		
Time to neutrophil engraftment, median (range)	29.0 (12, 56)	-
Duration of neutropenia, median (range)	20.5 (4, 48)	-
Platelet Engraftment (days)[d]		
Time to platelet engraftment, median (range)	43.5 (20, 200)	-
Splenectomized (N=16), median (range)	34.5 (20, 78)	-
Non-splenectomized (N=40), median (range)	46.0 (27, 200)	-
Time (days) to hospital discharge[e] , median (range)	39.0 (23, 110)	-
Duration (months) of follow-up after exa-cel, median (range)	38.1 (7.9, 67.1)	-

[a] Full Analysis Set includes participants who received exa-cel infusion as of Aug 2024. 48 participants have completed CLIMB THAL-111 and 47 are currently enrolled in CLIMB-131 (1 withdrew consent in 131-not due to an adverse event).
[b] Primary Efficacy Set includes participants who were followed for ≥16 months after exa-cel infusion and ≥14 months after completion of RBC transfusions for post-transplant support or TDT management (evaluable for the primary endpoint).
[c] Defined as the first day of 3 consecutive measurement of absolute neutrophil count ≥500 cells/μL on 3 different days.
[d] Defined as the first day of 3 consecutive measurement of unsupported (no platelet transfusion in last 7 days) platelet count ≥20,000/μL on 3 different days.
[e] Defined as the number of days from exa-cel infusion to hospital discharge following neutrophil engraftment.

exa-cel, exagamglogene autotemcel; **RBC,** red blood cell; **SD,** standard deviation; **TDT,** transfusion-dependent β-thalassemia.

Durable Increases in Total and Fetal Hemoglobin in TDT

Normal or Near Normal Levels of Total Hb

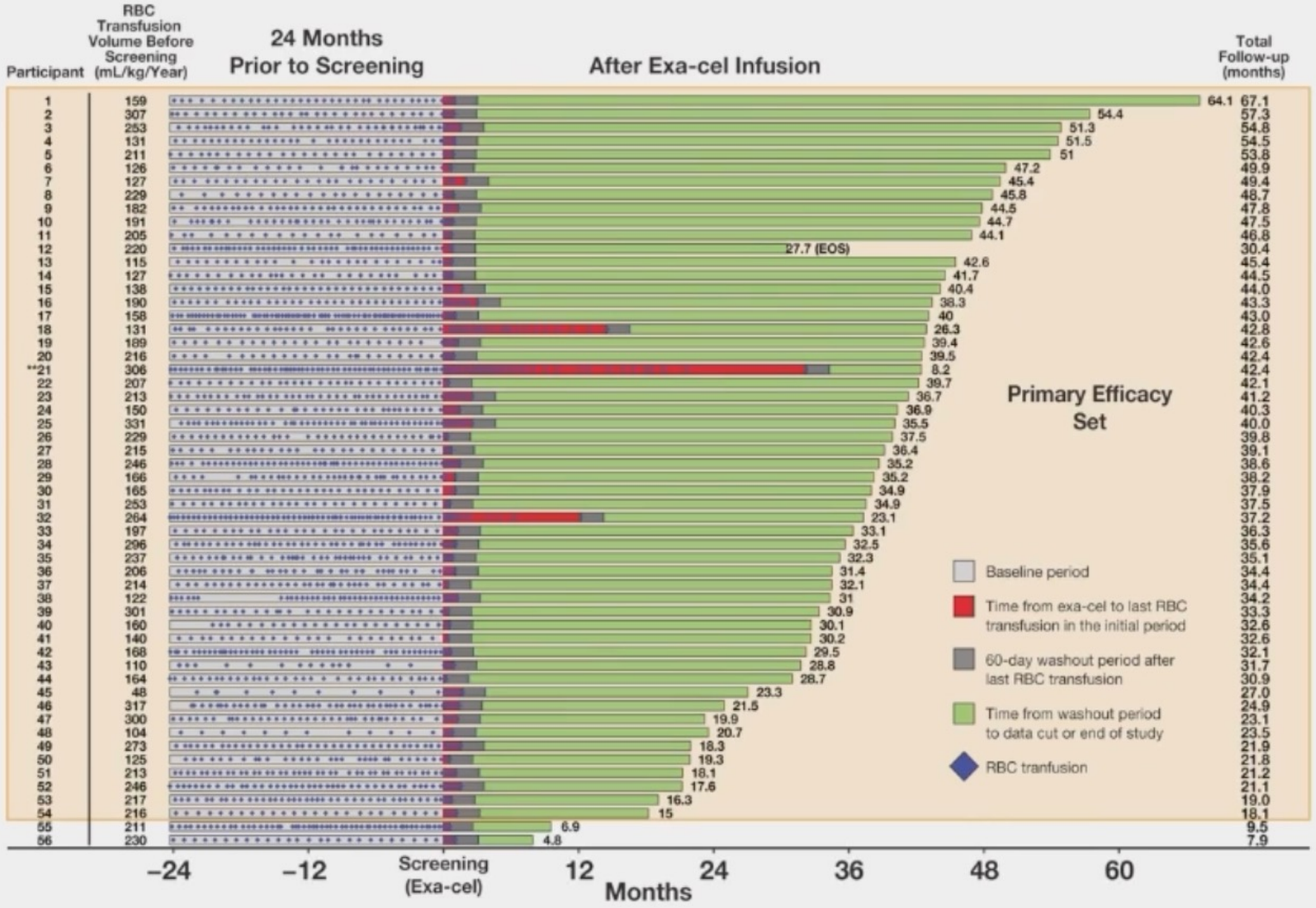


- Durable high (>95%) proportion of red blood cells containing HbF (F-cells) observed after exa-cel in TDT
- Similar results observed in CLIMB SCD-121 with all participants demonstrating a durable increase in total Hb to normal or near normal levels and fetal hemoglobin to ~40% with pancellular distribution after exa-cel (**Poster #4954**)

Data shown are based on the Full Analysis Set as of Aug 2024. Figures depict data for all timepoints where at least 5 participants have completed the specified visit.

BL, baseline; **Hb,** hemoglobin; **HbF,** fetal hemoglobin; **SE,** standard error; **TDT,** transfusion-dependent β-thalassemia; **SCD,** sickle cell disease.

TDT: Durable Transfusion Independence After Exa-cel (CLIMB THAL-111 and 131):
Transfusion Independence Achieved in 98% and Maintained for up to ~5 years



Durable transfusion independence achieved

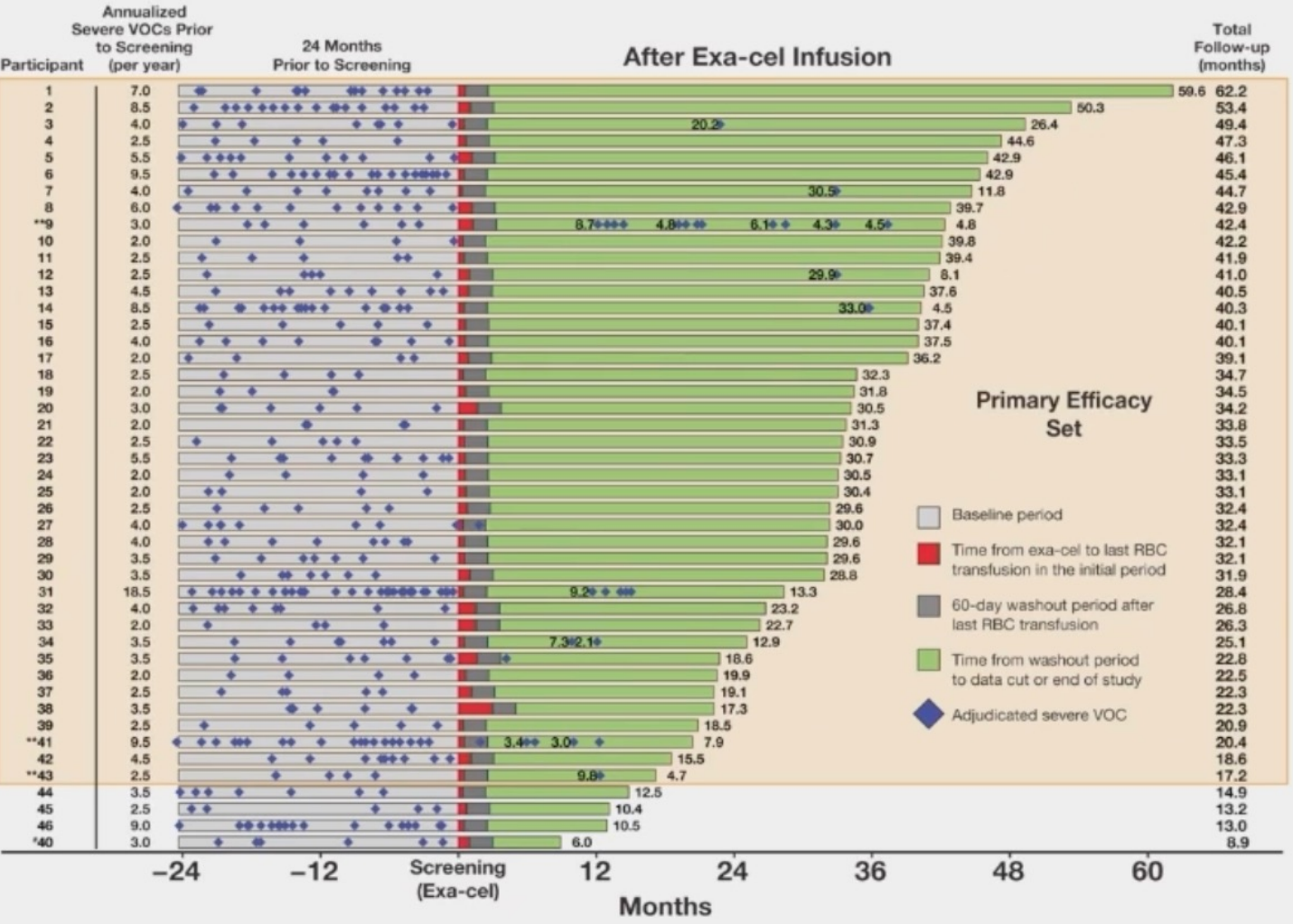
- 98% (53/54) of evaluable participants achieved TI12 in CLIMB THAL-111 and CLIMB-131 (95% CI: 90%, 100%)
- Mean duration of transfusion independence *34.5 months (range 15.0 to 64.1)*
- 1 participant who has not yet achieved TI12 has been transfusion free for the last 8.2 months

Data are shown for the Full Analysis Set. Primary Efficacy Set includes participants evaluable for the primary endpoint as of Aug 2024. 48 participants have completed CLIMB THAL-111, and 47 are currently enrolled in CLIMB-131 (1 withdrew consent in 131-not due to an adverse event).

EOS, end of study; **exa-cel**, exagamoglogene autotemcel; **RBC**, red blood cell; **TI12**: transfusion independent for ≥12 consecutive months while maintaining a weighted average hemoglobin ≥9 g/dL.

SCD: Durable VOC-Free After Exa-cel (CLIMB SCD-121 and 131)

93% achieved VF12 and Maintained for up to ~5 years



**participants who have not yet achieved VF12; #participant died from respiratory failure due to COVID-19 infection; not related to exa-cel.

Some participants had VOCs after the washout period; numerical values before the VOC indicate the number of months a participant was VOC-free since the washout period/previous VOC. Data shown are based on the Full Analysis Set as of Aug 2024. 34 participants have completed CLIMB SCD-121, and all 34 have enrolled in CLIMB-131.

exa-cel, exagamglogene autotemcel; **RBC**, red blood cell; **VF12**, free of severe VOCs for ≥12 consecutive months; **VOC**, vaso-occlusive crisis

Durable VOC-free benefit was achieved (Figure 3)

- 93% (39/42) of evaluable participants achieved VF12 in CLIMB SCD-121 or CLIMB-131 (95% CI: 81%, 99%)
- Mean duration of VOC-free
  30.9 months (range 12.9 to 59.6)

3 participants who have not yet achieved VF12 have significant clinical benefit:

- reduced hospitalization of 91%, 71%, and 100%
- no acute chest syndrome occurred post infusion

Pain events after exa-cel generally occurred in adult participants with a history of chronic pain and/or following an identifiable pain trigger such as:

- infection (e.g., parvovirus B19, influenza B, or COVID-19)
- procedure (e.g., bone marrow biopsy)
- corticosteroids

TDT: Exa-cel Safety Profile Is Consistent With Myeloablative Busulfan Conditioning and Autologous HSCT

AE Overview in CLIMB THAL-111	Exa-cel N = 56
Participants with	
Any AEs, n (%)	56 (100.0)
AEs related to exa-cel, n (%)[a]	16 (28.6)
AEs related to busulfan, n (%)[a]	55 (98.2)
AEs Grade 3/4, n (%)	50 (89.3)
SAEs, n (%)	19 (33.9)
SAEs related to exa-cel, n (%)[a,b]	2 (3.6)
AEs leading to death, n (%)	0
Any malignancies, n (%)	0

All participants engrafted neutrophils and platelets. Data are presented from exa-cel infusion to Month 24.
[a] Includes related and possibly related AEs (or SAEs). [b] SAEs previously reported in 2 participants and fully resolved. One participant had SAEs starting peri-engraftment and in context of HLH (HLH, acute respiratory distress syndrome, and headache were related to exa-cel; idiopathic pneumonia syndrome was related to exa-cel and busulfan). One participant had SAEs of delayed neutrophil engraftment and thrombocytopenia both related to exa-cel and busulfan (neutrophil engraftment achieved on Day 56 without use of backups cells).

In CLIMB THAL-131, of 47 participants enrolled, there were no new AEs related to exa-cel; 5 (10.6%) had new SAEs (none were related to exa-cel); no malignancies or deaths.

Common AE: Preferred Term in CLIMB THAL-111, n (%)	Exa-cel N = 56
Febrile neutropenia	34 (60.7)
Headache	31 (55.4)
Stomatitis	30 (53.6)
Thrombocytopenia	25 (44.6)
Anemia	25 (44.6)
Nausea	24 (42.9)
Mucosal inflammation	23 (41.1)
Vomiting	23 (41.1)
Abdominal pain	23 (41.1)

Table includes common AEs occurring in ≥40% of participants from exa-cel infusion through Month 24.

7 (12.5%) participants had VOD events

- all events were related to busulfan conditioning
- all events resolved after defibrotide treatment without any participant receiving ventilatory support or dialysis

Most AEs occurred in the first 6 months with rates decreasing over time; safety is consistent in adolescents and adults. Overall safety results consistent in SCD (Poster #4954)

shown are based on the Full Analysis Set as of Aug 2024.
adverse event; **exa-cel**, exagamglogene autotemcel; **HLH**, hemophagocytic lymphohistiocytosis; **HSCT**, hematopoietic stem cell transplantation; **SAE**, serious adverse event; **VOD**, venoocclusive liver disease.

Conclusions

- Exa-cel is the first and only approved CRISPR-Cas9 gene editing therapy
- Long-term follow-up to over 5 years demonstrates that all TDT and SCD participants achieved durable clinical benefits
  - TDT: 98% achieved transfusion independence
  - SCD: 93% achieved freedom from VOC
  - Consistent efficacy in adults and adolescents and across genotypes
  - Durable increases in HbF resulting in total hemoglobin at normal or near normal levels
  - Stable allelic editing in bone marrow and peripheral blood, demonstrates durable editing of long-term HSCs
- Clinically meaningful improvements in measures of iron overload and quality-of-life in TDT
- Safety profile in TDT consistent with myeloablative busulfan conditioning and autologous HSCT; no malignancies or deaths

Exa-cel benefit was durable and has the potential to provide a one-time functional cure

CRISPR-Cas9, clustered regularly interspaced short palindromic repeats-associated 9 nuclease; **exa-cel,** exagamglogene autotemcel; **HbF,** fetal hemoglobin; **HSCs,** hematopoietic stem cells; **HSCT,** hematopoietic stem cell transplantation; **TDT,** transfusion-dependent β-thalassemia; **SCD,** sickle cell disease; **VOC,** vaso-occlusive crisis.

513 Initial Results from the BEACON Clinical Study: A Phase 1/2 Study Evaluating the Safety and Efficacy of a Single Dose of Autologous CD34+ Base Edited Hematopoietic Stem Cells (BEAM-101) in Patients with Sickle Cell Disease with Severe Vaso-Occlusive Crises

Gupta AO, et al.

Ex-vivo base editing into the promoter of the *HBG1/2* gene that encodes γ-globin
to disrupt BCL11A transcriptional repressor binding site, leading to increased HbF production
No double-stranded DNA breaks

Patients 18-35 yrs with severe SCD (≥ 4 VOC in the 2-yr period prior to screening)
6 patients dosed, 3 one single mobilization cycle, 3 two mobilization cycles (plerixafor)
Mean BEAM-101 dose: 11.9 x 10^6 (5.2-23.4) viable CD34+ cells/kg
4 patients with > 1 month of Follow-up
Neutrophil and platelet engraftement at a median of 17 (15-19) and 20 (11-34) days respectively
One patient died from respiratory failure likely related to busulfan conditioning

- Hb: 11.0-18.2 g/dl at life time point (LTP)
- HbF : 60% at LTP
- % F-cells were 99.6% in P1 at M6, 94.4% in P2 at M4, 52.0% in P3 at M2, and 13.3% in P4 at M1 with all patients having >19 pg HbF/F-cell at LTP
- Peripheral blood editing in nucleated cells, measured in P1 (at M6) and P2 (at M3), was 69.9% and 76.1%, respectively
- Markers of hemolysis (lactate dehydrogenase, indirect bilirubin, haptoglobin, and reticulocyte counts) have normalized or improved for all patients

No VOCs have been reported by investigators following BEAM-101 treatment.

NEJM Evidence

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ORIGINAL ARTICLE

Hydroxyurea for Children and Adults with Hemoglobin SC Disease

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Y. Dei-Adomakoh

Prospective Identification of Variables as Outcomes for Treatment (PIVOT)

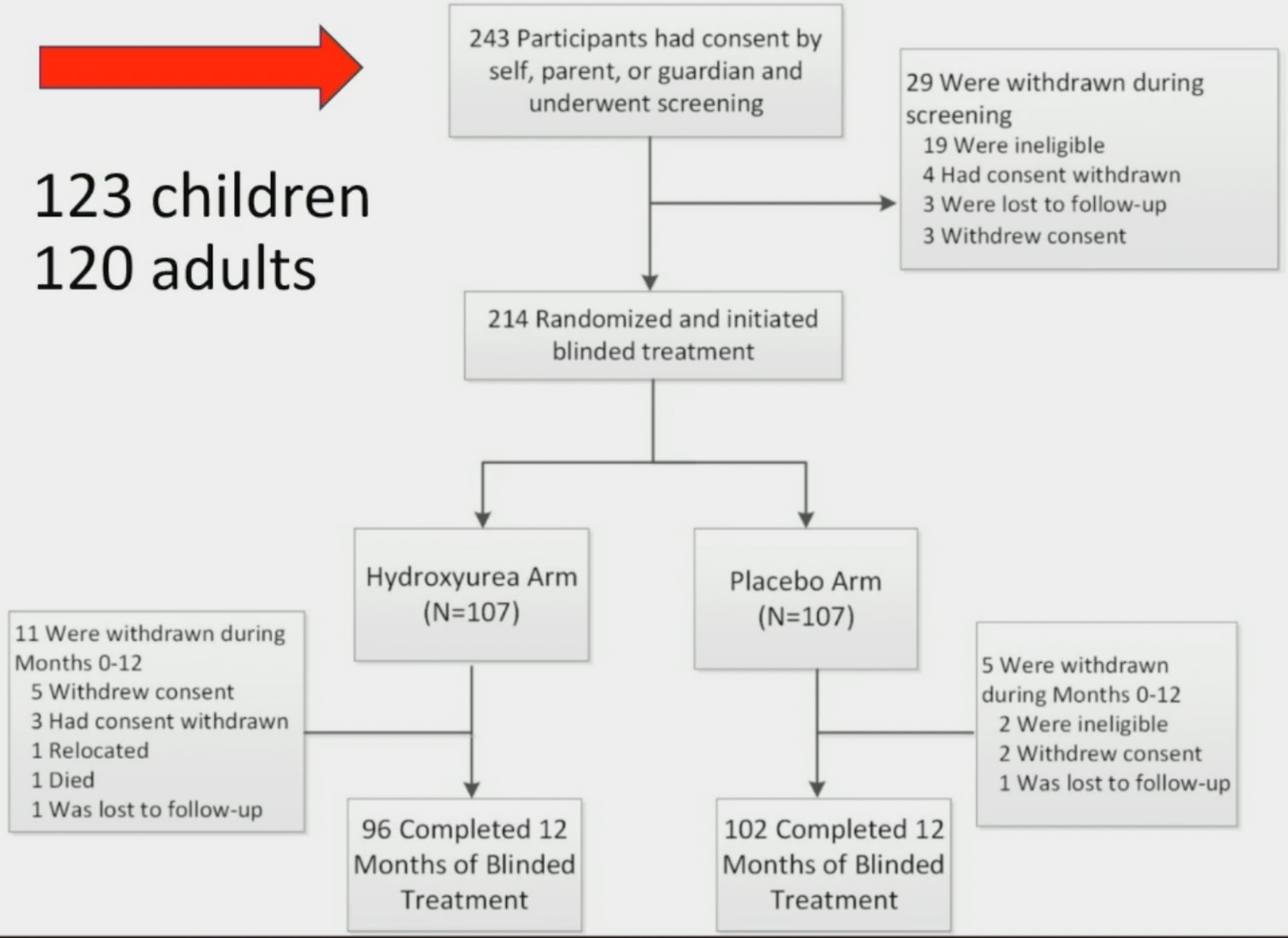
- Double-blind, placebo-controlled Phase 2 trial
- 100 children, 100 adults with HbSC disease
- Age 5-50 years
- 20 mg/kg hydroxyurea vs placebo for 12 months
- Two opportunities for dose escalation
- Open-label continuation if deemed safe

Cincinnati Children's
changing the outcome together

Study Endpoints

- Primary: dose-limiting toxicities in each treatment arm
  - Non-inferiority design (15% threshold)
  - Cytopenia and high hemoglobin (> 12.0 g/dL, ≥ 1.0 g/dL increase)
- Secondary: laboratory effects, clinical adverse events
  - CBC, reticulocytes, Hb quantification (HbF, S, C)
  - Sickle cell-related events, hospitalizations, malaria

123 children
120 adults



Dose Limiting Toxicities

	Hydroxyurea			Placebo			Difference (95% CI)
	Pediatric N = 56	Adult N = 51	All N = 107	Pediatric N = 56	Adult N = 49	All N = 105	All
All DLT (% pts)	20	47	33	4	18	11	22 (11 – 34)
Thrombocytopenia	5	33	19	0	2	1	18 (9 – 26)
Neutropenia	4	24	13	0	0	0	13 (6 – 20)
High Hemoglobin	13	10	11	4	16	10	2 (-7 – 11)
Anemia	0	0	0	0	0	0	-
Reticulocytopenia	0	1	1	0	0	0	-

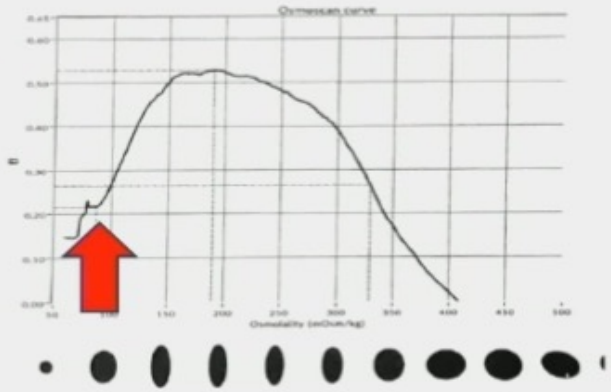
Clinical Adverse Events (per 100 person-years)

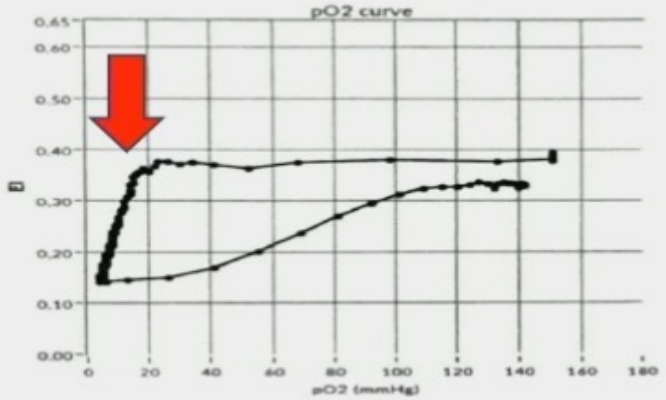
	Hydroxyurea			Placebo			IRR (95% CI)
	Pediatric N = 56	Adult N = 51	All N = 107	Pediatric N = 56	Adult N = 49	All N = 105	All
All Clinical AE	284.6	218.1	253.8	358.1	340.2	349.8	0.70 (0.48-0.92)
Vaso-occlusive pain	44.1	71.9	57.0	137.0	164.4	149.6	0.38 (0.28-0.52)
Malaria	30.1	32.3	31.2	27.4	52.5	39.0	0.80 (0.47-1.35)
Hospitalization	12.0	13.9	12.9	23.5	38.8	30.6	0.42 (0.22-0.81)
Any sickle related (N)	18	19	37	33	36	69	0.39 (0.26-0.59)

Exploratory Laboratory Analyses

	Hydroxyurea Treatment		
	Baseline	Month 12	Change
OsmoScan, Omin	98 ± 18	108 ± 36	12 ± 38
OxygenScan, point-of-sickling (mm Hg)	19.0 ± 7.2	15.7 ± 5.5	-2.9 ± 8.8
Viscosity at shear rate of 75 s^{-1} (cP)	5.54 ± 1.12	5.04 ± 0.74	-0.46 ± 1.08
Viscosity at shear rate of 300 s^{-1} (cP)	4.68 ± 0.72	4.34 ± 0.50	-0.31 ± 0.65

Omin





Point-of-sickling

Summary and Conclusions

- The placebo-controlled Phase 2 PIVOT trial was successfully conducted in Ghana, where HbSC is prevalent and causes morbidity and mortality
- Hydroxyurea treatment at 20mg/kg/day was associated with more DLT than placebo, all asymptomatic, mild, transient and reversible
- Measurable benefits were observed in hematological parameters
- Associated with fewer clinical adverse events
- Hydroxyurea may provide effective disease-modifying therapy for HbSC

Abstract #179

Etavopivat Reduces Incidence of Vaso-Occlusive Crises in Patients with Sickle Cell Disease: HIBISCUS Trial Phase 2 Results Through 52 Weeks

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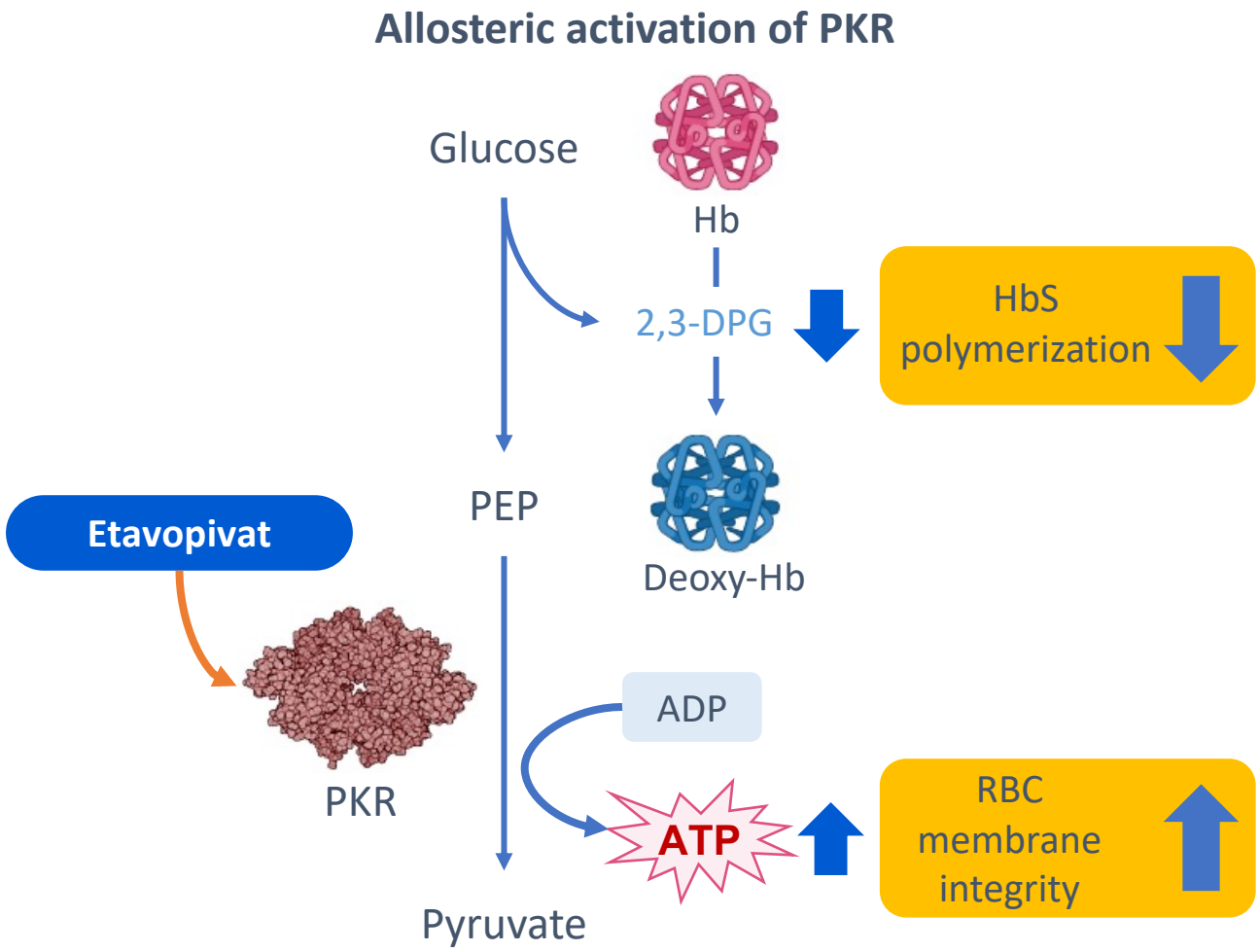
Presentation at the 66th ASH Annual Meeting and Exposition, December 7–10, 2024, San Diego, California, USA

Etavopivat: multimodal mechanism of action



- In a phase 1 study in **patients with SCD**, etavopivat therapy over 12 weeks resulted in a:
  - Rapid and sustained increase in Hb levels
  - Decrease in markers of hemolysis[1]

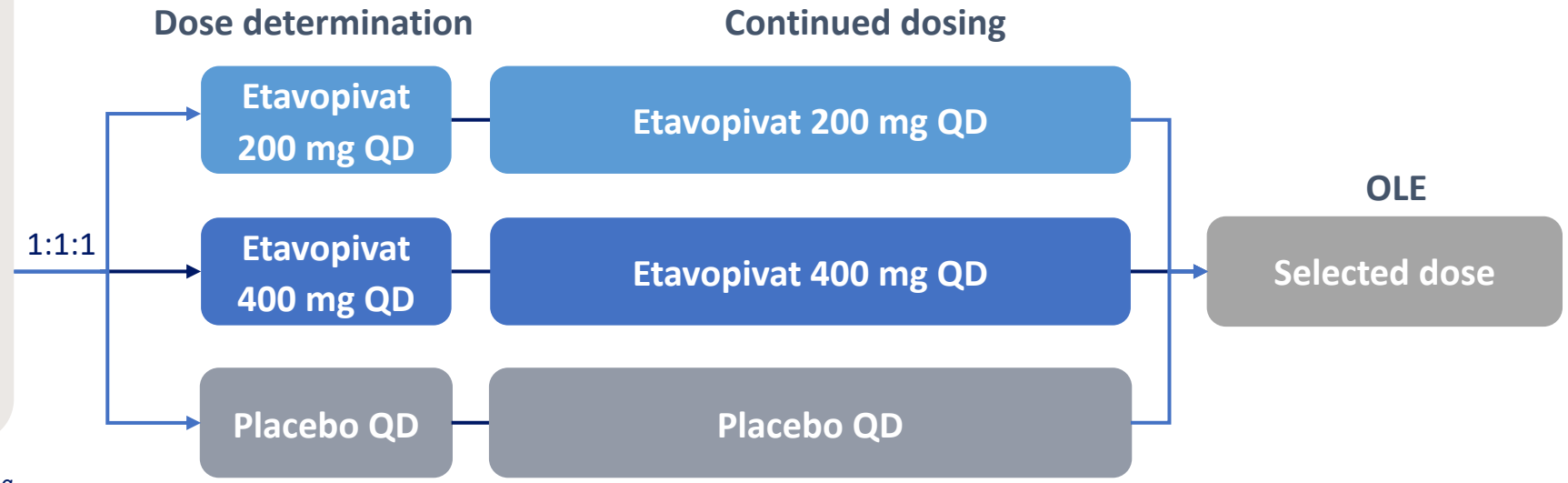
ADP, adenosine diphosphate; ATP, adenosine triphosphate; DPG, diphosphoglycerate; Hb, hemoglobin; HbS, sickle hemoglobin; PEP, phosphoenolpyruvate; PKR, RBC pyruvate kinase isozyme; RBC, red blood cell; SCD, sickle cell disease.

1. Saraf SL et al. Blood Adv 2024;8:4459–75.

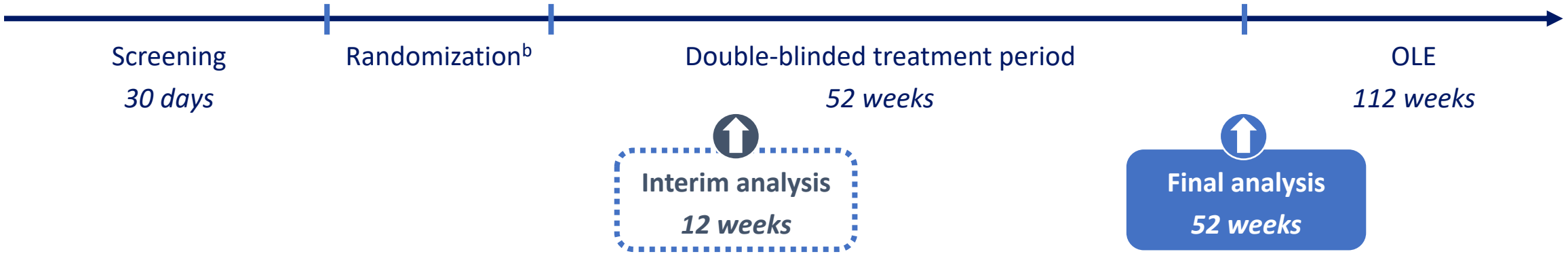
HIBISCUS: Phase 2 dose determination study design

Key inclusion criteria

- Aged 12–65 years
- Any SCD genotype
- Hb level ≥5.5 to ≤10.5 g/dL
- 2–10 VOCs requiring a medical setting visit in the previous 12 months
- Stable dosing with standard-of-care treatments: HU (≥90 days prior), crizanlizumab, or L-glutamine (≥12 months prior[a])



VOC definition: VOC requiring a visit in a medical setting (including hospital, clinic, emergency department, day hospital, home visit, or telemedicine visit), including the following subtypes: uncomplicated VOC; acute chest syndrome; hepatic sequestration; splenic sequestration; priapism



[a]Must have been ≥80% compliant with the planned regimen.
[b]Stratified by: age (12–17 or 18–65 years); number of VOCs in the preceding 12 months (2–3 or 4–10); use of HU, crizanlizumab, l-glutamine in the previous 12 months (yes or no).
Hb, hemoglobin; HU, hydroxyurea; OLE, open-label extension; QD, once daily; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

HIBISCUS: Endpoints and analysis populations

Primary endpoints

- Annualized VOC rate over 52 weeks based on independently adjudicated review[a]
- Hb response (>1 g/dL increase from baseline) at Week 24[b]

Secondary endpoints

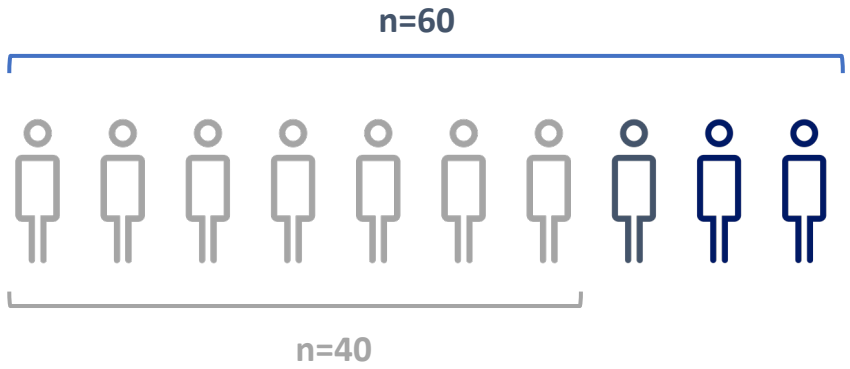
- Change from baseline in hemolysis biomarkers (absolute reticulocyte count, indirect bilirubin, and lactate dehydrogenase) at Week 24
- Change from baseline in Hb at Week 52 during the blinded treatment period
- Time to first VOC
- Change from baseline in PROMIS Fatigue Scale score[c] at Week 52

Safety endpoints

- Adverse events, clinical laboratory tests, physical examinations, and other clinical measures

Analysis populations included

Intent to treat:
All participants randomized



Per protocol:
- ≥80% protocol compliance
- Completion of the double-blind period
- No major protocol deviations impacting efficacy assessments

[a]Adjudicated in a blinded manner by a VOC Review Committee, comprising physicians experienced in the treatment of SCD.
[b]Using the mean of Hb measurements at Weeks 16, 20, and 24.
[c]Using PROMIS Fatigue Form 7a (≥18 years of age) and the Pediatric Fatigue short form 10a (12–17 years of age).
Hb, hemoglobin; PROMIS, Patient-Reported Outcomes Measurement Information System; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

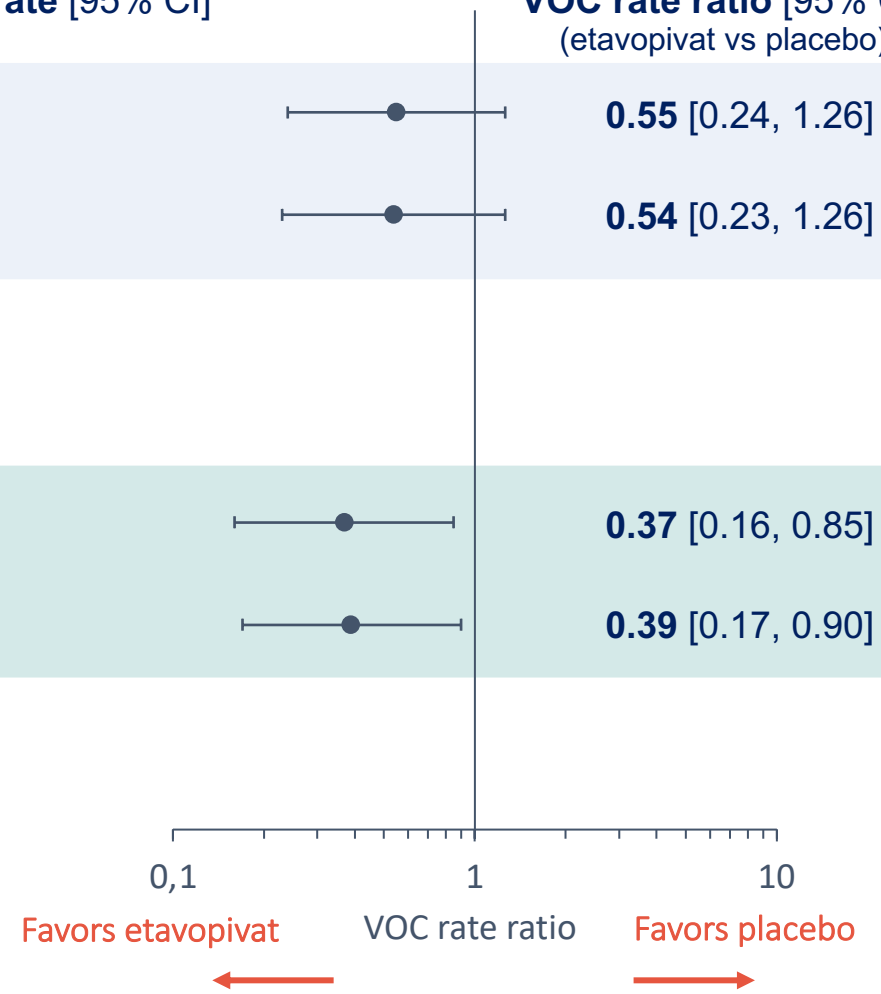
HIBISCUS: Demographics and baseline characteristics

	Etavopivat 200 mg/day (n=21)	Etavopivat 400 mg/day (n=20)	Placebo (n=19)
Age (years), mean (min., max.)	35.7 (14, 57)	34.0 (12, 59)	30.6 (13, 57)
Adolescents, n (%)	3 (14.3)	2 (10.0)	2 (10.5)
Female, (%)	17 (81.0)	14 (70.0)	10 (52.6)
Male, n (%)	4 (19.0)	6 (30.0)	9 (47.4)
Hispanic or Latino, n (%)	5 (23.8)	6 (30.0)	0
Black or African American, n (%)	13 (61.9)	15 (75.0)	16 (84.2)
Europe, n (%)	4 (19.0)	3 (15.0)	5 (26.3)
Middle East, n (%)	3 (14.3)	0	1 (5.3)
North America, n (%)	14 (66.7)	17 (85.0)	13 (68.4)
VOC frequency in year prior to study, mean (min., max.)	**3.0 (2, 7)**	**3.5 (2, 9)**	**3.3 (2, 9)**
2–3, n (%)	15 (71.4)	14 (70.0)	13 (68.4)
4–10, n (%)	6 (28.6)	6 (30.0)	6 (31.6)
Baseline Hb (g/dL)[a]			
Mean (SD)	**8.16 (1.17)**	**8.26 (1.07)**	**8.78 (1.20)**
Median (min., max.)	8.13 (5.9, 10.3)	8.50 (6.0, 9.8)	8.85 (6.6, 10.6)
Hb SS, n (%)	**18 (85.7)**	**18 (90.0)**	**18 (94.7)**
Hb SC, n (%)	1 (4.8)	1 (5.0)	1 (5.3)
Hb S-β^+ thalassemia, n (%)	1 (4.8)	0	0
Hb S-β^0 thalassemia, n (%)	1 (4.8)	1 (5.0)	0

[a]Average of Hb value at screening and Day 1.
Hb, hemoglobin; max., maximum; min., minimum; SD, standard deviation; VOC, vaso-occlusive crisis.

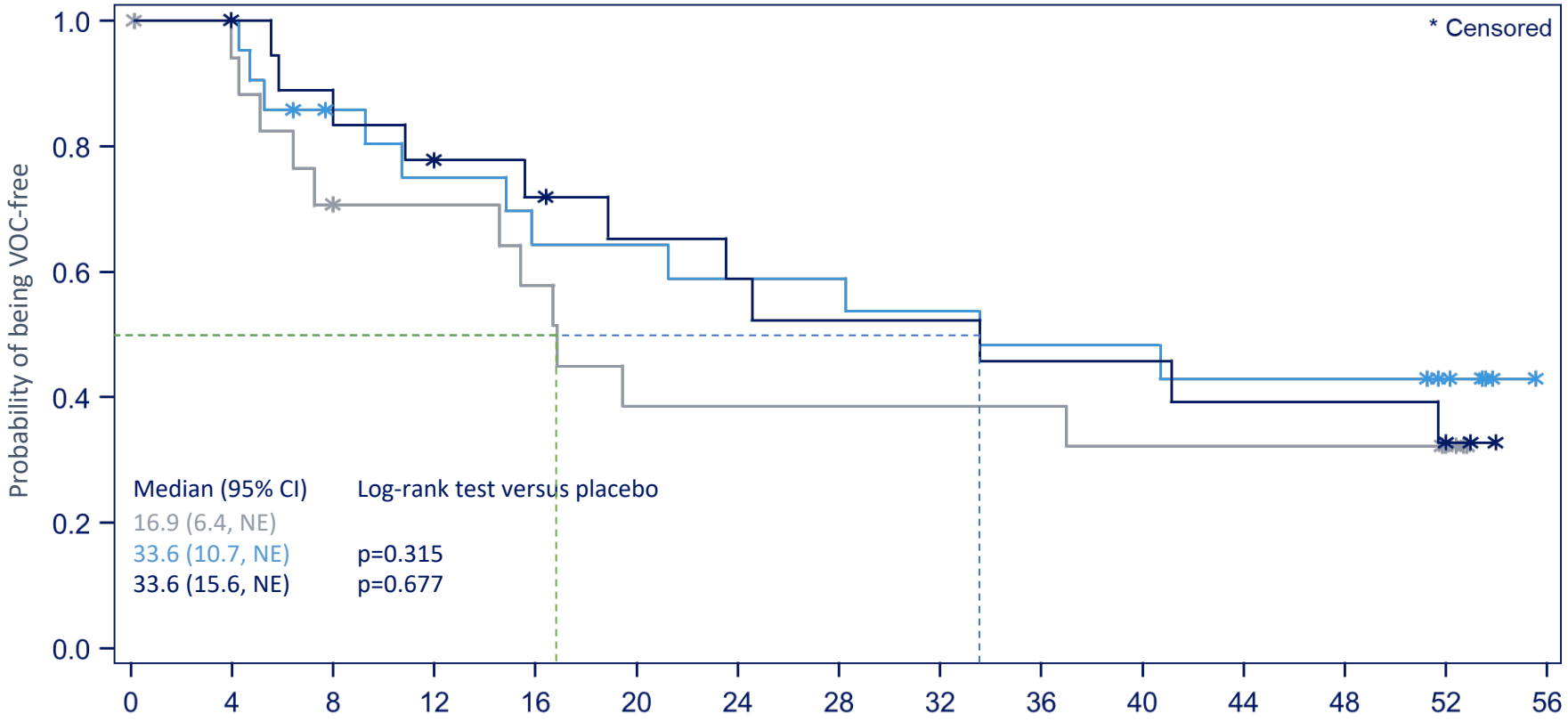
HIBISCUS: Annualized adjudicated VOC rate

		Annualized VOC rate [95% CI]	**VOC rate ratio** [95% CI] (etavopivat vs placebo)	**Reduction**	**P-value**
ITT population	**Etavopivat 200 mg** (n=21)	**1.07** [0.49, 2.37]	**0.55** [0.24, 1.26]	**45%**	0.154
	Etavopivat 400 mg (n=20)	**1.06** [0.46, 2.46]	**0.54** [0.23, 1.26]	**46%**	0.154
	Placebo (n=19)	**1.97** [0.89, 4.36]			
PP population	**Etavopivat 200 mg** (n=13)	**0.66** [0.28, 1.58]	**0.37** [0.16, 0.85]	**63%**	0.020
	Etavopivat 400 mg (n=12)	**0.70** [0.29, 1.66]	**0.39** [0.17, 0.90]	**61%**	0.028
	Placebo (n=15)	**1.77** [0.90, 3.50]			



Adjudicated in a blinded manner by a VOC Review Committee, comprising physicians experienced in the treatment of sickle cell disease.
Negative binomial model for VOC events, based on a generalized linear model with treatment group as fixed effect and the natural log of the duration (years) of study treatment exposure.
CI, confidence interval; ITT, intent-to-treat; PP, per-protocol; VOC, vaso-occlusive crisis.

HIBISCUS: Time to first adjudicated VOC

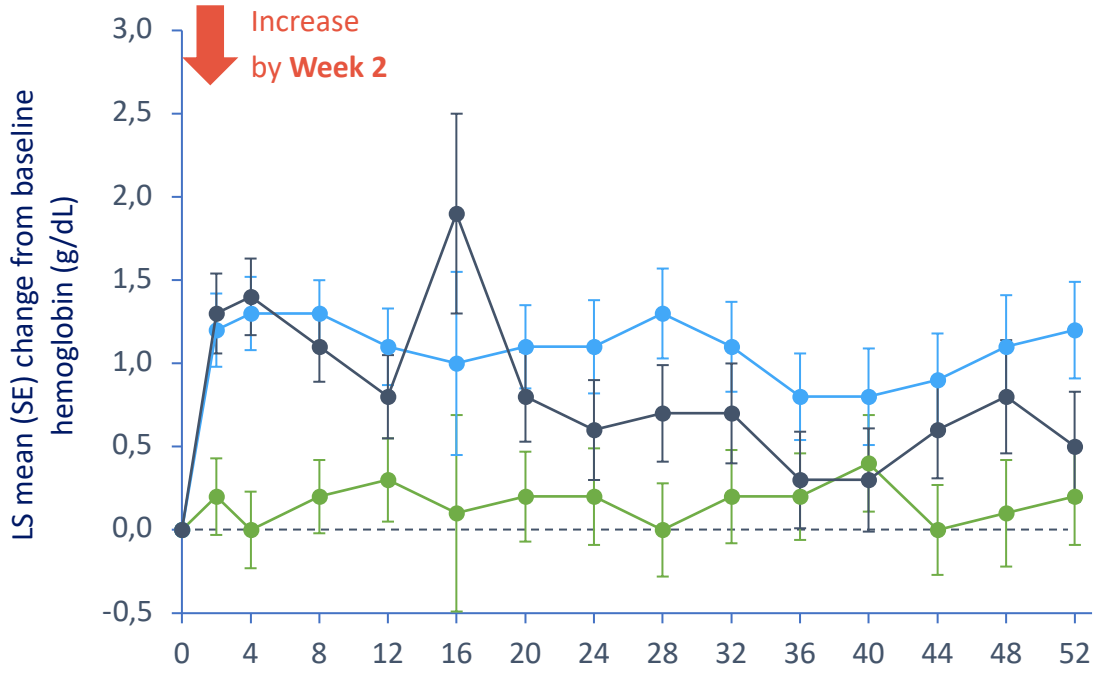


ITT population:															
Placebo (n=19)	19	17	12	11	9	6	6	6	6	6	5	5	5	4	0
Etavopivat 200 mg (n=21)	21	21	16	14	12	12	11	11	10	9	9	8	8	6	0
Etavopivat 400 mg (n=20)	20	20	16	14	12	10	9	8	8	7	7	6	6	5	0

Adjudicated in a blinded manner by a VOC Review Committee, comprising physicians experienced in the treatment of sickle cell disease.
CI, confidence interval; ITT, intent-to-treat; NE, not estimable; VOC, vaso-occlusive crisis.

HIBISCUS: Hemoglobin response (increase >1 g/dL) at Week 24 and change in hemoglobin concentration over time

	Etavopivat 200 mg/day	Etavopivat 400 mg/day	Placebo
ITT population	n=21	n=20	n=19
Hb responders at Week 24, %	**38.1**	**25.0**	**10.5**
Rate difference vs placebo	27.6	14.5	
p-value	p=0.187	p=0.660	
PP population	n=13	n=12	n=15
Hb responders at Week 24, %	**46.2**	**33.3**	**13.3**
Rate difference vs placebo	32.8	20.0	
p-value	p=0.248	p=0.680	

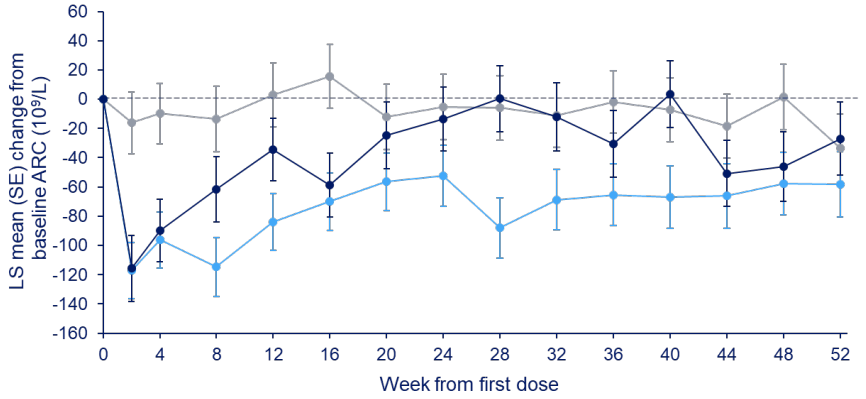


ITT population:														
Placebo (n=19)	16	17	13	15	15	13	15	14	15	16	15	16	13	13
Etavopivat 200 mg (n=21)	20	19	17	18	17	17	14	15	15	14	14	12	14	13
Etavopivat 400 mg (n=19)	14	15	14	15	14	12	13	12	10	11	11	12	10	9

Hb response: >1 g/dL increase from baseline (using the mean of Hb measurements at Weeks 16, 20, and 24); one-sided p-value was obtained from an exact Cochran-Mantel-Haenszel general association test between the indicated etavopivat group versus placebo and stratified by the randomization stratification factors; the test was considered statistically significant if one-sided p-value <0.025. LS mean change from baseline hemoglobin: the mixed model for repeated measures was based on change from baseline and includes a random effect for patient and fixed effects for treatment group, baseline, randomization stratification factors (age, prior/concomitant treatment, vaso-occlusive crisis), nominal study visit, and treatment group by visit interaction.
Hb, hemoglobin; ITT, intent-to-treat; PP, per-protocol; LS, least square; SE, standard error.

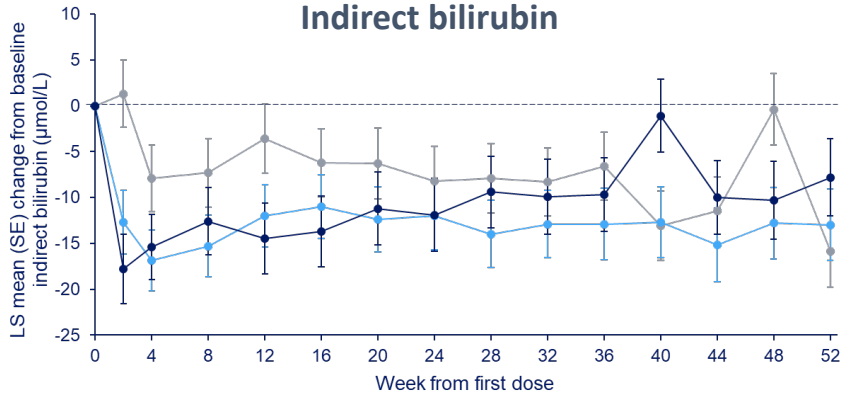
HIBISCUS: Changes in markers of hemolysis

Absolute reticulocyte count



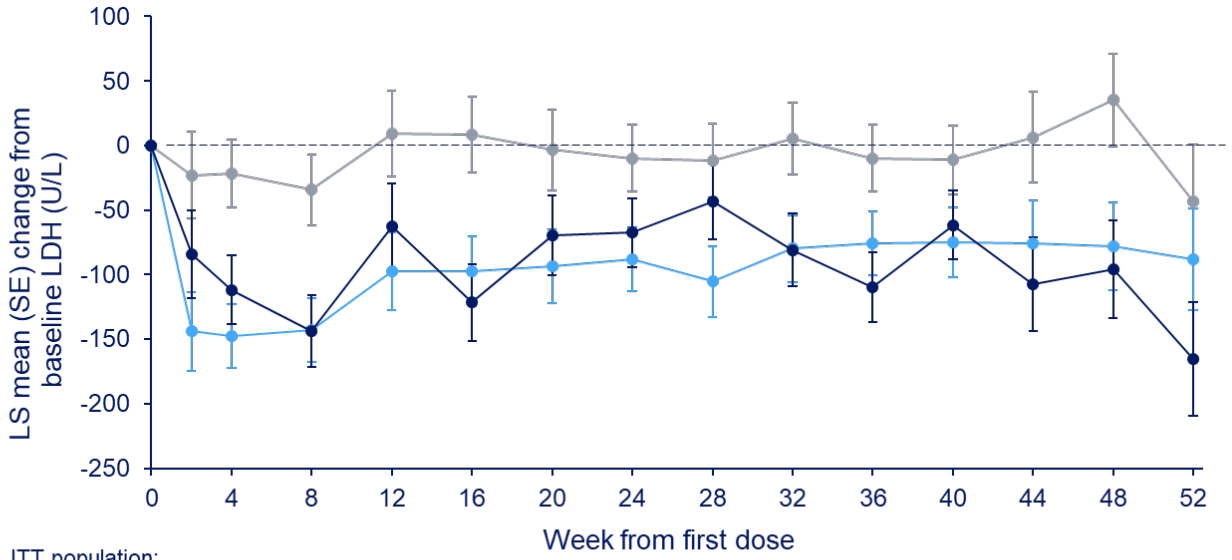
ITT population:														
Placebo (n=18)	14	16	12	13	13	12	12	13	12	15	13	14	12	11
Etavopivat 200 mg (n=20)	19	18	15	18	17	17	13	14	15	14	14	12	14	12
Etavopivat 400 mg (n=18)	12	14	12	14	13	11	13	12	10	11	11	12	10	9

Indirect bilirubin



Placebo (N=19)	16	17	15	15	16	14	15	15	16	16	15	16	14	14
Etavopivat 200 mg (N=20)	18	20	19	19	18	17	15	16	16	14	14	13	14	14
Etavopivat 400 mg (N=21)	15	18	16	14	14	13	13	14	12	13	13	13	11	12

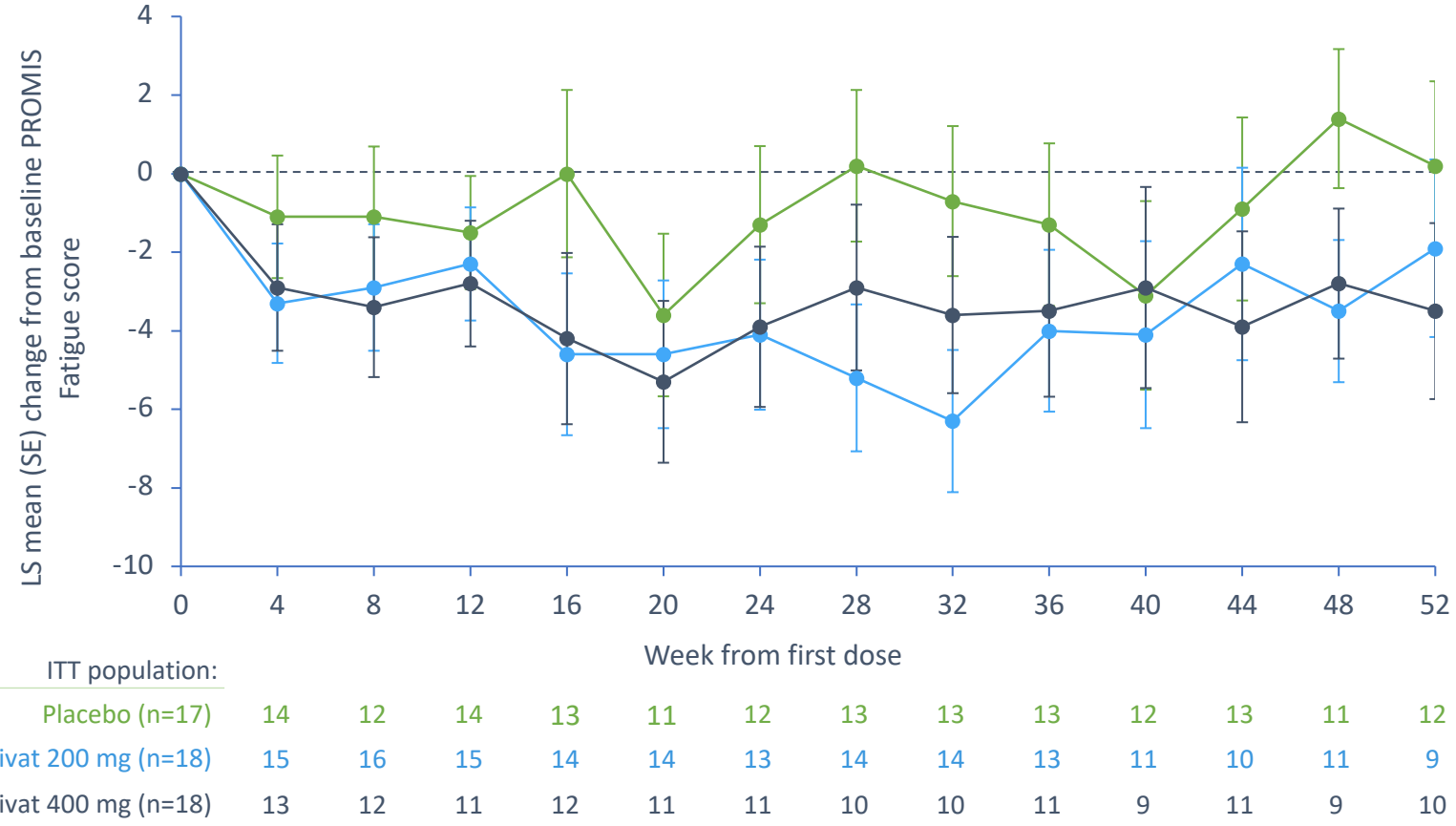
Lactate dehydrogenase



ITT population:														
Placebo (n=18)	12	16	11	14	15	12	14	14	13	15	13	14	13	11
Etavopivat 200 mg (n=21)	17	20	19	20	18	16	16	15	15	14	12	13	13	14
Etavopivat 400 mg (n=19)	14	17	14	15	15	14	12	13	12	13	13	12	10	12

The repeated measures model is based on change from baseline and includes a random effect for patient and fixed effects for treatment group, baseline, randomization stratification factors (age, prior/concomitant treatment, vaso-occlusive crisis), nominal study visit, and treatment group by visit interaction.
ARC, absolute reticulocyte count; ITT, intent-to-treat; LDH lactate dehydrogenase; LS, least square; SE, standard error.

HIBISCUS: Change in PROMIS Fatigue score



ITT population:													
Placebo (n=17)	14	12	14	13	11	12	13	13	13	12	13	11	12
Etavopivat 200 mg (n=18)	15	16	15	14	14	13	14	14	13	11	10	11	9
Etavopivat 400 mg (n=18)	13	12	11	12	11	11	10	10	11	9	11	9	10

LS mean (95% CI) difference from placebo at Week 52

Etavopivat 200 mg/day	Etavopivat 400 mg/day
–2.1 (–8.5, 4.3)	–3.7 (–10.1, 2.7)
p=0.502	p=0.243

Using PROMIS Fatigue Form 7a (≥18 years of age).
The repeated measures model is based on change from baseline and includes a random effect for patient and fixed effects for treatment group, baseline, randomization stratification factors (prior/concomitant treatment, and vaso-occlusive crises), nominal study visit, and treatment group by visit interaction.
CI, confidence interval; ITT, intent-to-treat; LS, least square; PROMIS, Patient-Reported Outcome Measurement Information System; SE, standard error.

HIBISCUS: Summary of treatment-emergent adverse events

	Etavopivat 200 mg/day (n=21) n (%) Events[a]	Etavopivat 400 mg/day (n=20) n (%) Events[a]	Placebo (n=19) n (%) Events[a]
Any TEAE	17 (81.0) 139	18 (90.0) 124	18 (94.7) 135
TEAEs reported as VOCs	11 (52.4) 32	13 (65.0) 25	12 (63.2) 39
Deaths	**0**	**0**	**0**
Serious TEAEs	5 (23.8) 5	4 (20.0) 5	3 (15.8) 3
TEAE leading to drug discontinuation	2 (9.5) 2	0	0
TEAE requiring a dose hold/interruption	4 (19.0) 7	2 (10.0) 2	4 (21.1) 4
Select TEAEs[b]			
Sickle cell anemia with crisis (as reported by the investigator)	**8 (38.1) 18**	**14 (70.0) 32**	**14 (73.7) 48**
Nausea	**3 (14.3) 5**	**2 (10.0) 2**	**2 (10.5) 2**
Headache	**2 (9.5) 4**	**3 (15.0) 6**	**2 (10.5) 3**
Urinary tract infection	**4 (19.0) 5**	**1 (5.0) 1**	**0**
Vomiting	**2 (9.5) 2**	**2 (10.0) 5**	**1 (5.3) 1**
Insomnia	**0**	**3 (15.0) 4**	**0**
ALT increased	1 (4.8) 3	2 (10.0) 2	0
AST increased	1 (4.8) 2	2 (10.0) 2	0
Diarrhea	1 (4.8) 1	2 (10.0) 2	0
Constipation	2 (9.5) 3	0	3 (15.8) 3
GGT increased	0	2 (10.0) 2	0
Dyspepsia	1 (4.8) 1	0	2 (10.5) 2

[a]Number of events. [b]TEAEs considered relevant to the disease or drug's mechanism of action.
ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; TEAE, treatment-emergent adverse event; VOC, vaso-occlusive crisis.

HIBISCUS: Serious adverse events

	Etavopivat 200 mg/day (n=21)	Etavopivat 400 mg/day (n=20)	Placebo (n=19)
SAE, n (%)	**5 (23.8)**	**4 (20.0)**	**3 (15.8)**
SAEs of relevance[a], n (%) Events[b]			
Possibly drug related			
Hepatic enzyme increased	**1 (4.8) 1**	0	0
Hb decreased	0	**1 (5.0) 1**	0
Unlikely drug related			
Cerebrovascular accident	**1 (4.8) 1**	0	0
Pulmonary embolism coincided with COVID-19	0	**1 (5.0) 2**	0

The **cerebrovascular accident** and **hepatic enzyme increased** led to permanent discontinuation of the study drug

[a]SAEs of relevance comprise those considered possibly related to study drug or of relevance to the disease. [b]Number of events. All SAEs resolved or resolved with sequelae, and most SAEs were deemed unrelated to the study drug by the investigator.
All other SAEs: COVID-19, urinary tract infection, urinary retention in the 200 mg group; bile duct stone, tibia fracture in the 400 mg group; COVID-19, appendicitis, hypoxia in the placebo group.
Hb, hemoglobin; SAE, serious adverse event.

HIBISCUS: Summary

- Based on pharmacokinetics, pharmacodynamics, and dose–efficacy response modeling analysis using 12-week data, the Data and Safety Monitoring Board selected the **400 mg/day dosage** of etavopivat for study in confirmatory phase 3 trials
- Etavopivat was well tolerated, and no unexpected safety issues were identified
- Compared with placebo, daily use of etavopivat in the ITT population resulted in the following positive trends:
  - **Lower annualized VOC rates through Week 52** (**200 mg** p=0.154, **400 mg** p=0.154)
  - **Delayed time to first VOC** (**200 mg** p=0.315, **400 mg** p=0.677)
  - **Early increases in Hb levels by Week 2 and increases in Hb response rates at Week 24** (**200 mg** p=0.187, **400 mg** p=0.660)
  - **Decreases in PROMIS Fatigue score at Week 52** (**200 mg** p=0.502, **400 mg** p=0.243)
  - **Decreases in hemolysis markers**
- These results are consistent with improved Hb-O_2 affinity and RBC health with oral etavopivat in SCD

Hb, hemoglobin; ITT, intention-to-treat; PROMIS, Patient-Reported Outcome Measurement Information System; RBC, red blood cell; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

Grazie !