# 66th ASH® Annual Meeting and Exposition

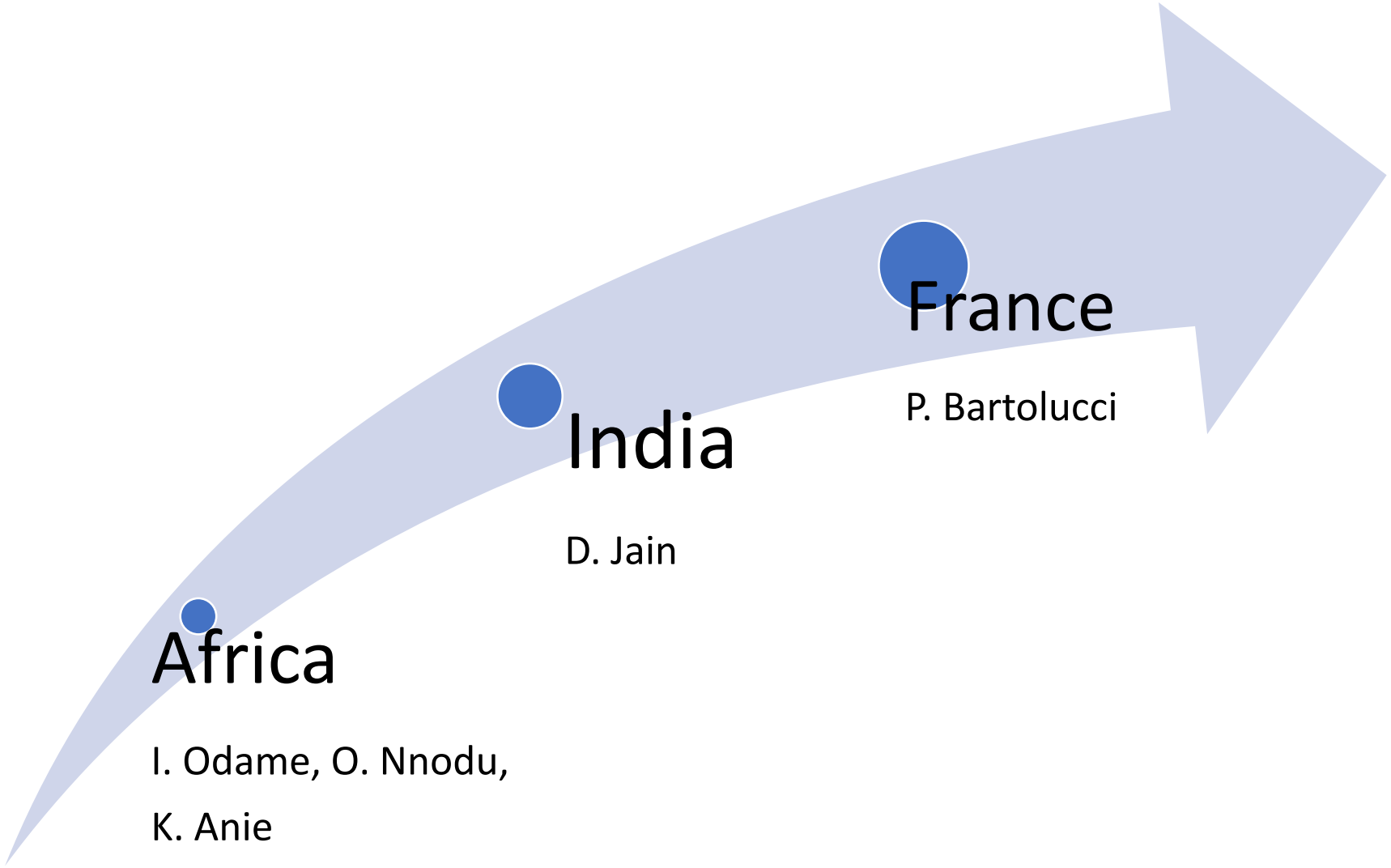
San Diego, December 7-10, 2024

Mariane de Montalembert

# Agenda

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

# Presentations on the management of SCD in different settings

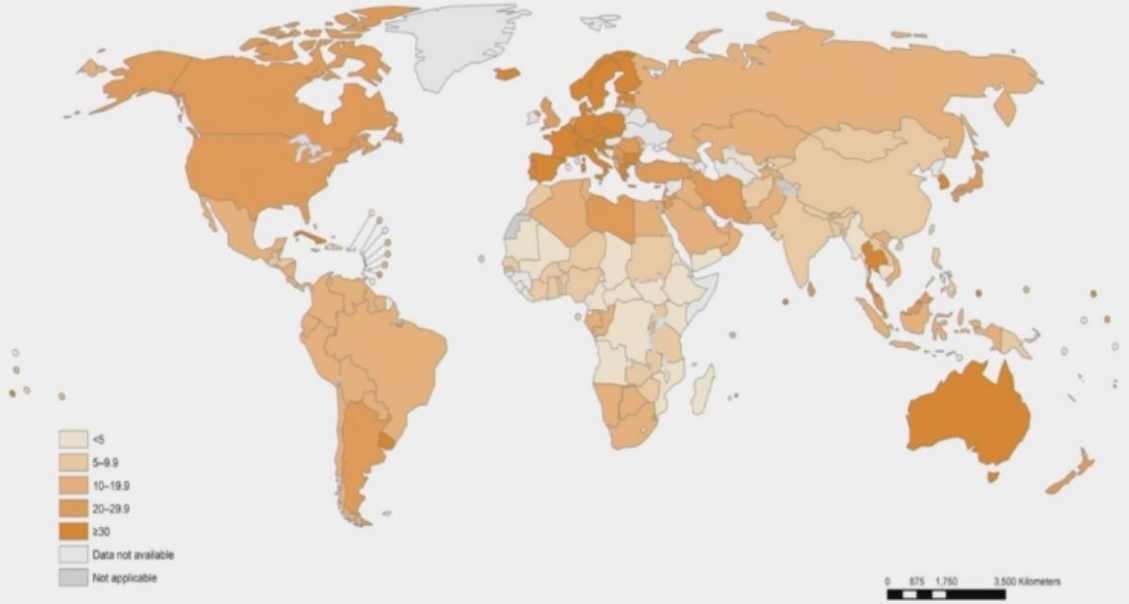


# Causes of SCD-related mortality in sub-Saharan Africa

- 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

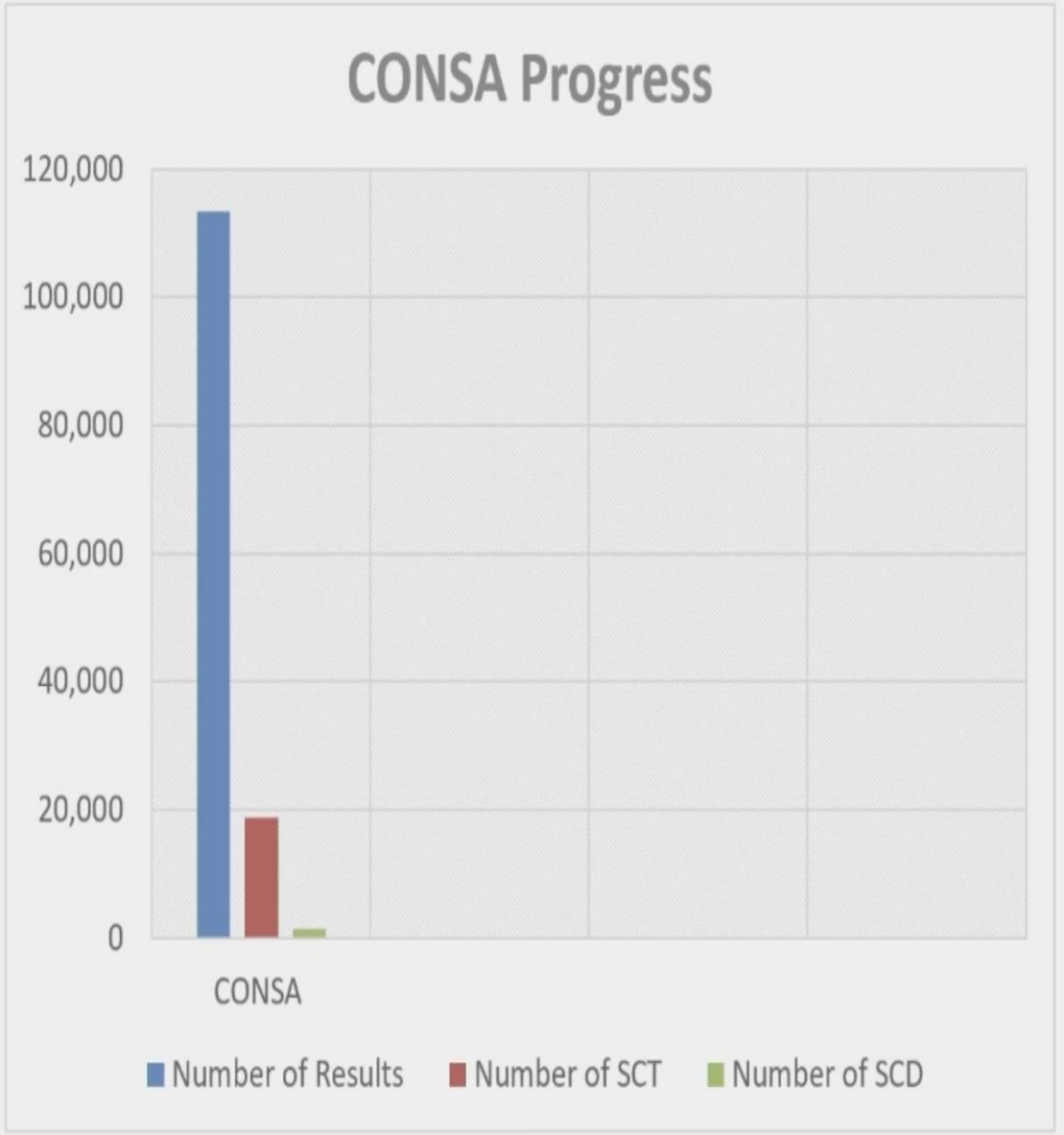
## Initiatives to Enhance NBS -I Consortium on Newborn Screening in Africa (CONSA)


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

**1992**

– Penicillin
– Cellulose acetate

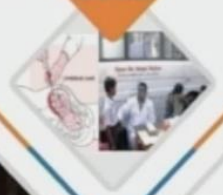
**1998**

**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

**2004 2005**

Prenatal Diagnosis

**2016**

Documentation/ publication on indian sickle cell Disease

**2018**

Curative Therapies HSCT for sickle cell Disease

**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

**2023**

Launched the (NSCAE)

**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 voxelator, 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

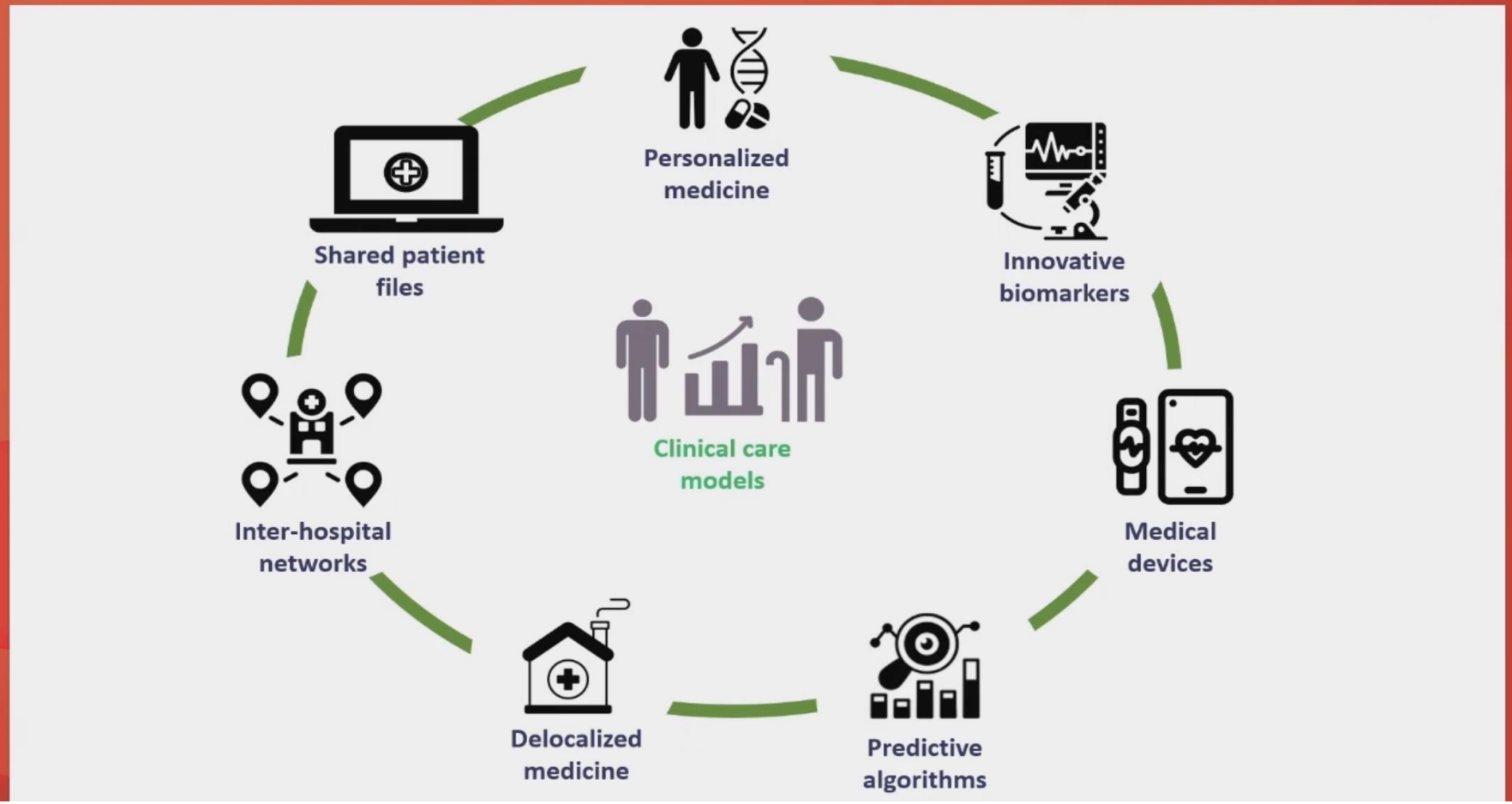
## National Sickle Cell Anaemia Elimination Mission



### 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**

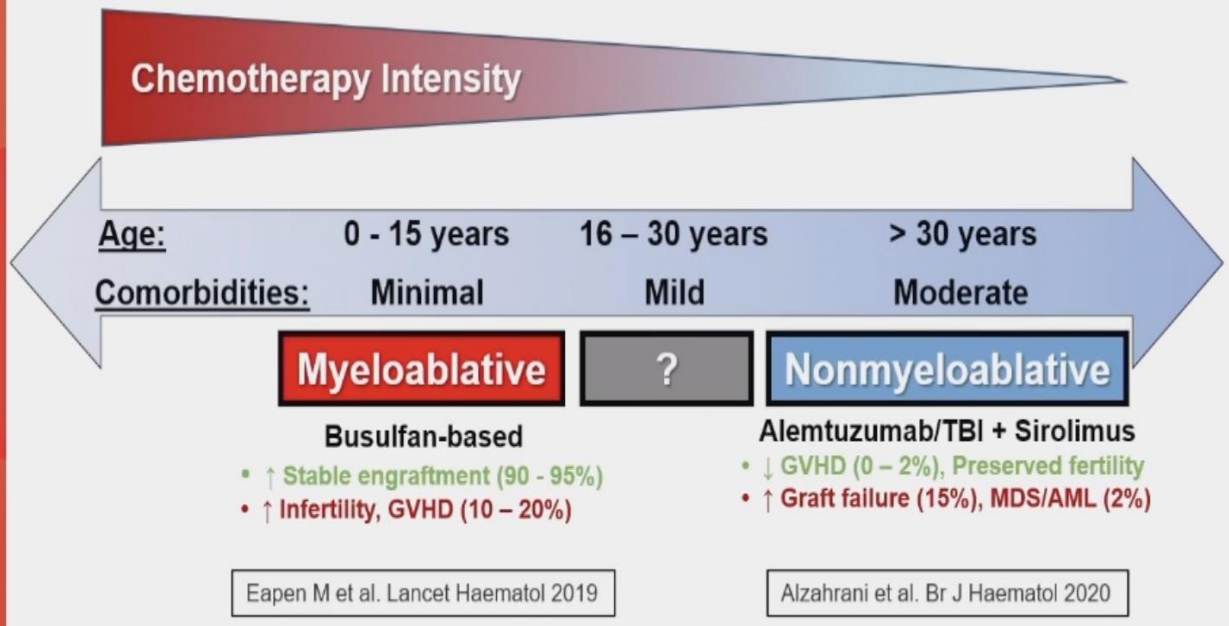
**Multidisciplinary meetings**

# 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




Eapen M et al. Lancet Haematol 2019

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

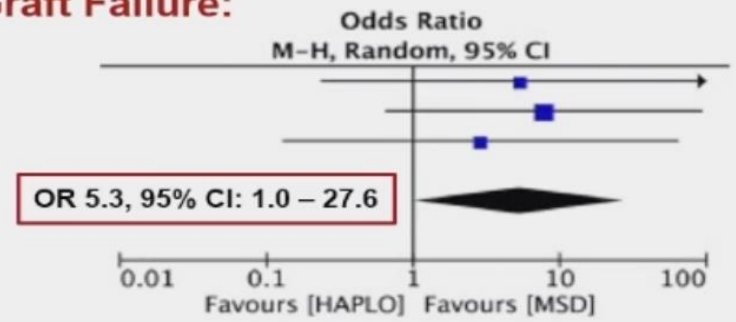
UI Health | UIC


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%) |

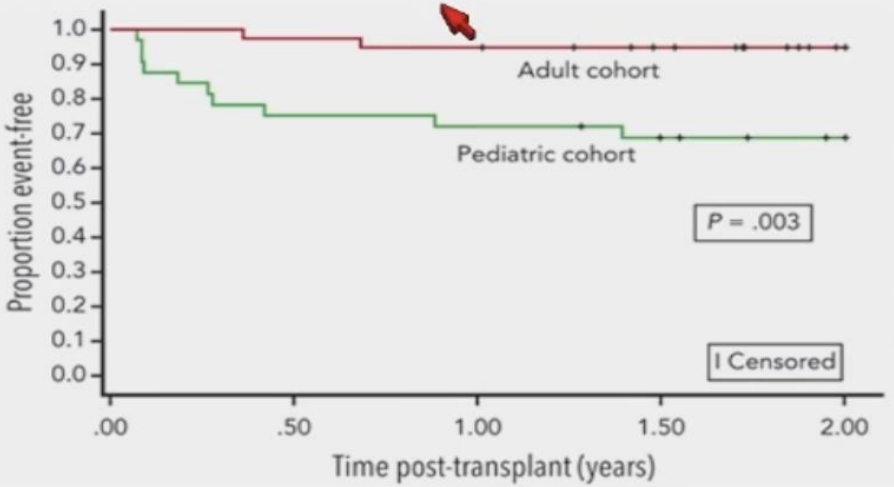
Aydin M et al. *Transplant & Cell Therapy* 2021

**Phase 2, Multicenter Trial**

+ Thiotepa to Johns Hopkins haplo regimen

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

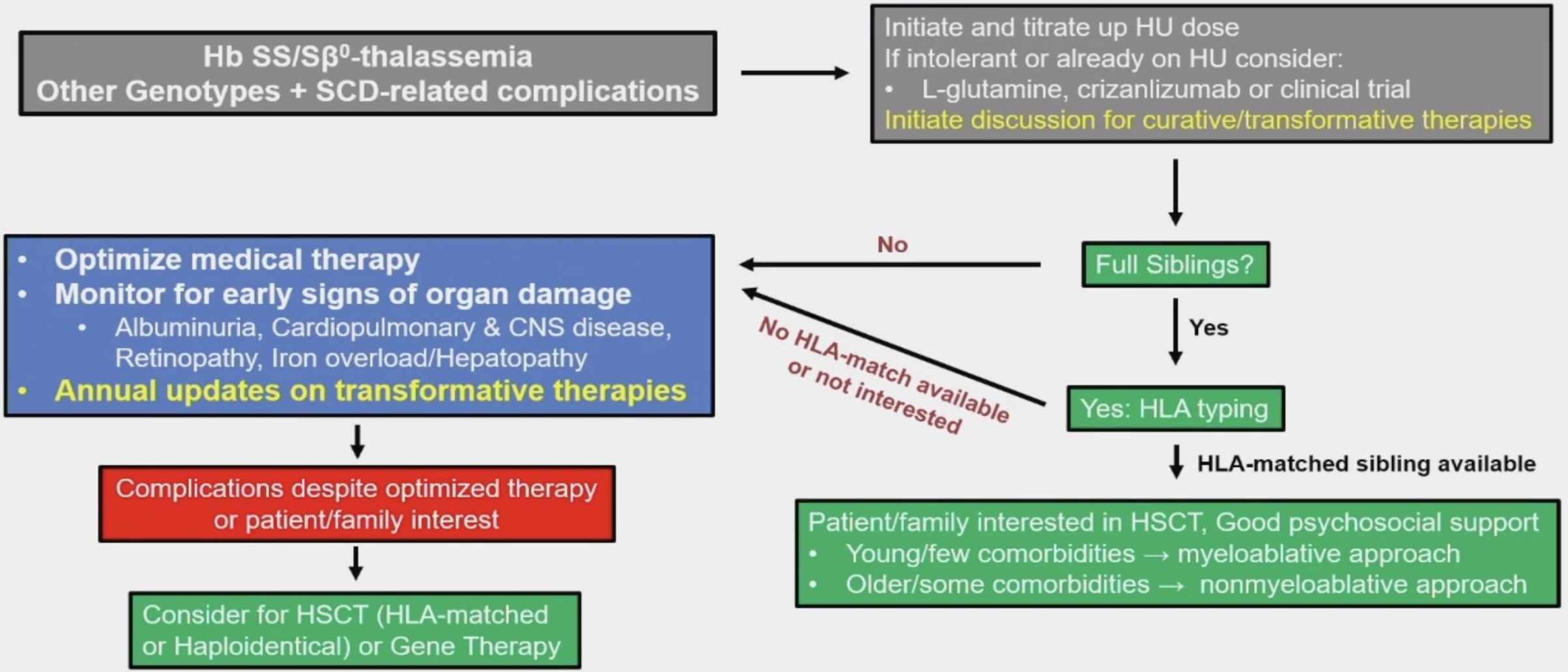
**Infection-related mortality:** **7%**
**Moderate-severe cGVHD:** **10%**; 19% children, 3% adults
**Event-free survival:** **89%;** 68% children, 95% adults
**2-Yr overall survival:** **94%;** 94% children, 95% adults




Kassim A et al. *Blood* 2024

UI Health | UIC

# My Approach for patients with SCD



# Gene Therapy for Sickle Cell Disease

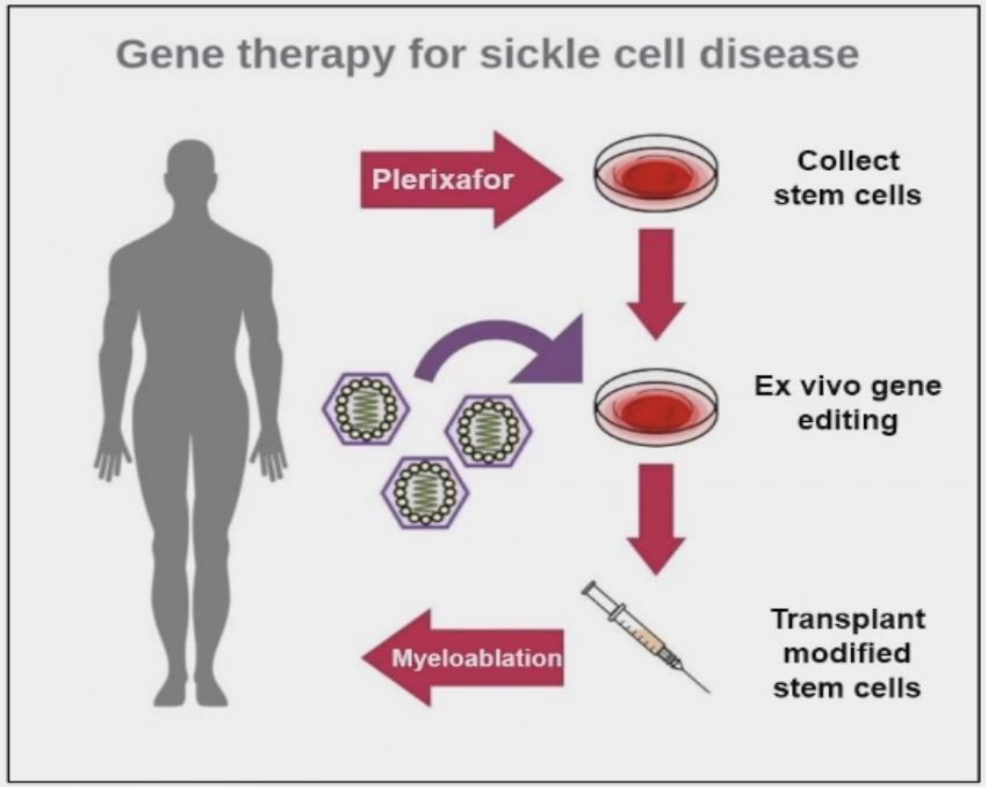



Figure adopted from NHLBI

| | 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<br>Stroke history excluded | VOC ≥ 4/year (no cap)<br>14% (5/35) stroke history<br>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, LYFGENIA™ (lovotibeglogene autotemcel) Qualified Treatment Center Locator, Authorized Treatment Center Locator | CASGEVY® (exagamglogene autotemcel), 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

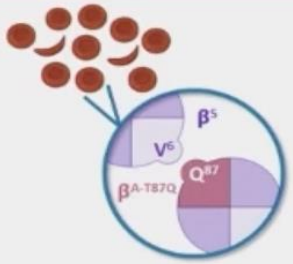
*Presenting author. **Former employee of bluebird bio, Inc.

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]

**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)

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

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

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

**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 (%)** | |
| $\beta^S/\beta^S$ | 55 (94.8) |
| $\beta^S/\beta^0$ | 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<br>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)

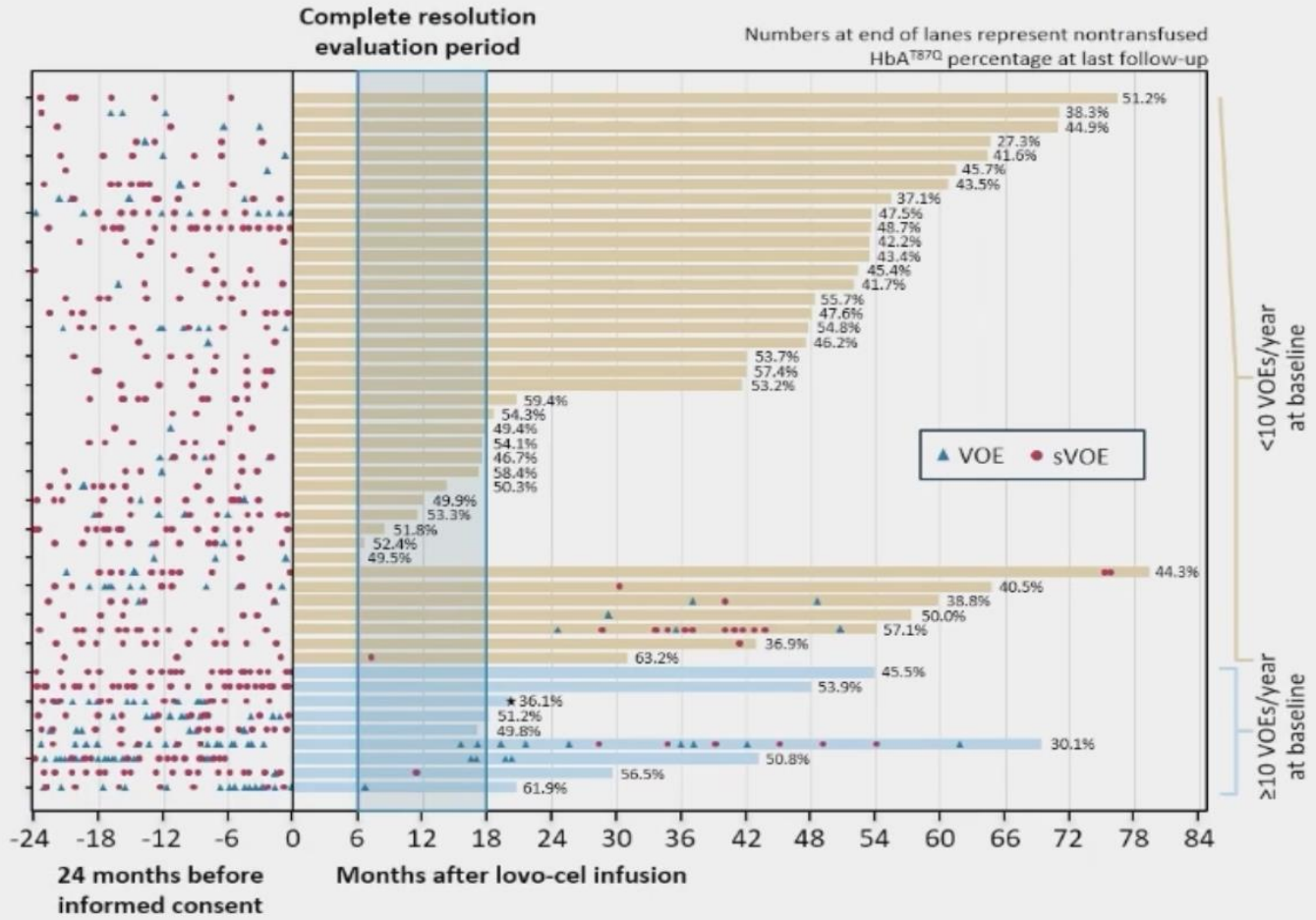
| | Total N=58 |
|---|---|
| **TEAEs, n (%)** | |
| **Any grade** | 58 (100) |
| **Grade ≥3** | 56 (96.6) |
| **Lovo-cel–related AEs,[a] n (%)** | **4 (6.9)** |
| **Anemia[b,c]** | 2 (3.4) |
| **Abdominal discomfort** | 1 ( 1.7) |
| **Blood pressure diastolic decreased** | 1 (1.7) |
| **Myelodysplastic 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 $\beta^S/\beta^S$ 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

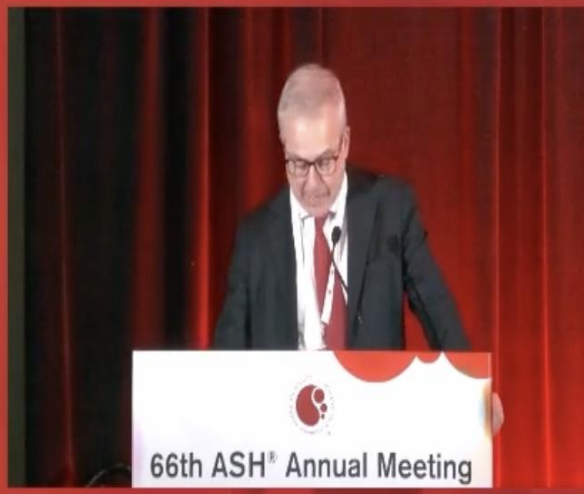
Data as of July 2024

# 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

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# TDT: Key Demographic Characteristics and Treatment Features

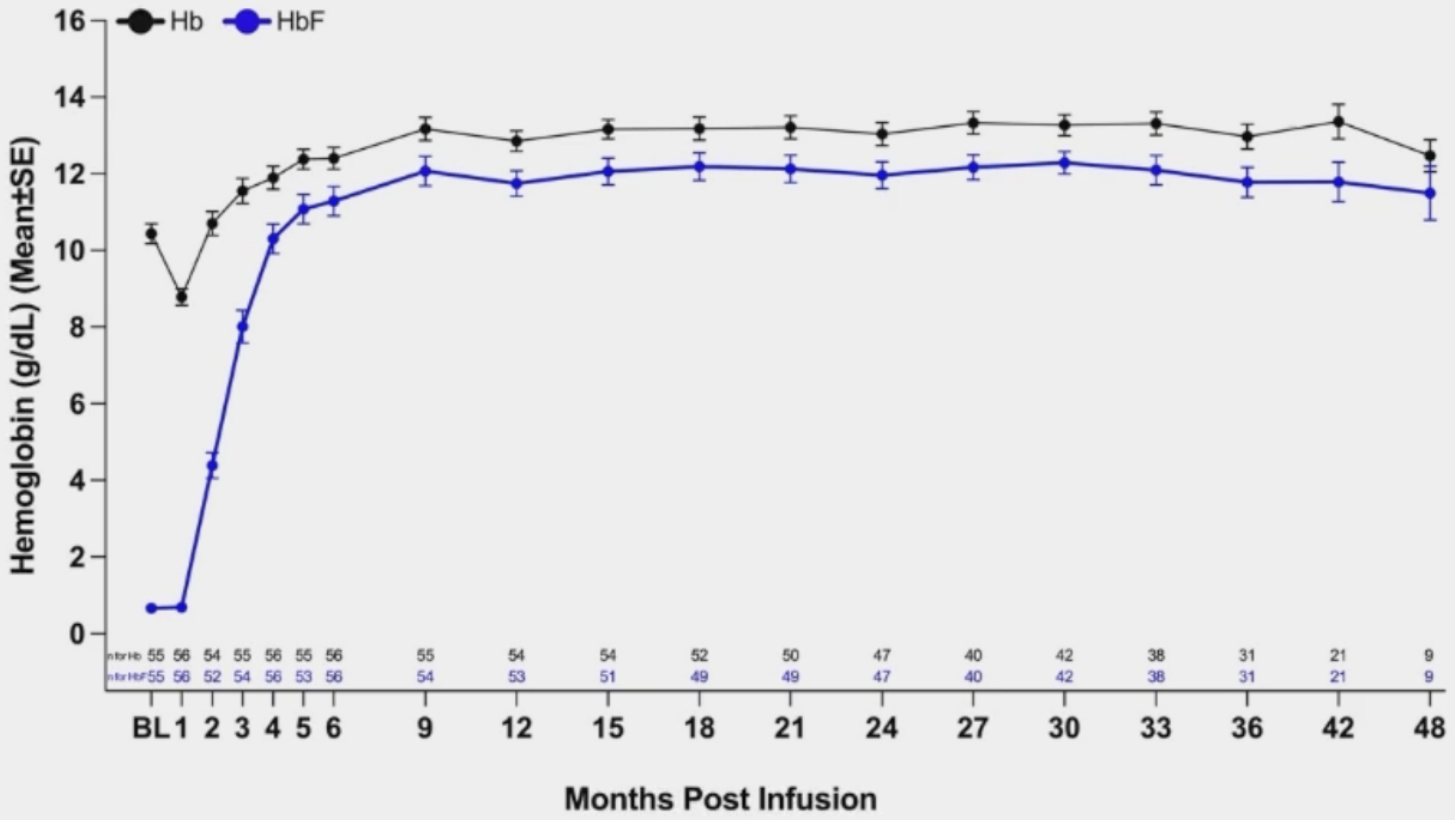
| | Full Analysis Set[a] N = 56 | Primary Efficacy Set[b] N = 54 |
|---|---|---|
| **Age (years) at screening, mean (SD)** | 21.2 (6.5) | 21.3 (6.6) |
| ≥12 and <18 years, n (%) | 20 (35.7) | 19 (35.2) |
| ≥18 and ≤35 years, n (%) | 36 (64.3) | 35 (64.8) |
| **Genotype, n (%)** | | |
| $\beta^0/\beta^0$ | 22 (39.3) | 21 (38.9) |
| $\beta^0/\beta^0$-like ($\beta^0$/IVS-I-110; IVS-I-110/IVS-I-110) | 13 (23.2) | 12 (22.2) |
| Non-$\beta^0/\beta^0$-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*

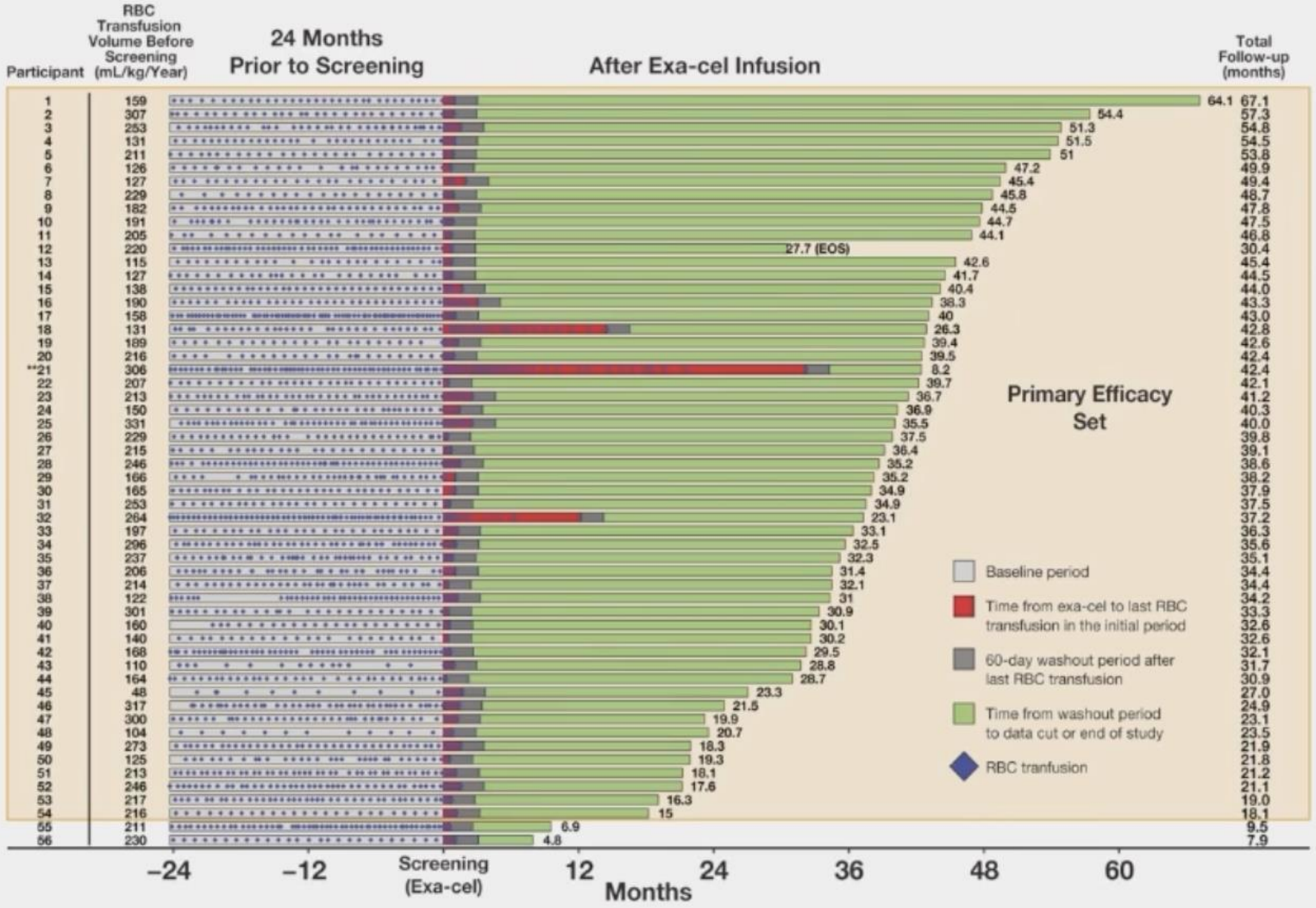



- Durable high (>95%) proportion of red blood cells containing HbF (F-cells) observed after exa-cel in TDT
- Similar results observed in CLIMB SCD-121 with all participants demonstrating a durable increase in total Hb to normal or near normal levels and fetal hemoglobin to ~40% with pancellular distribution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

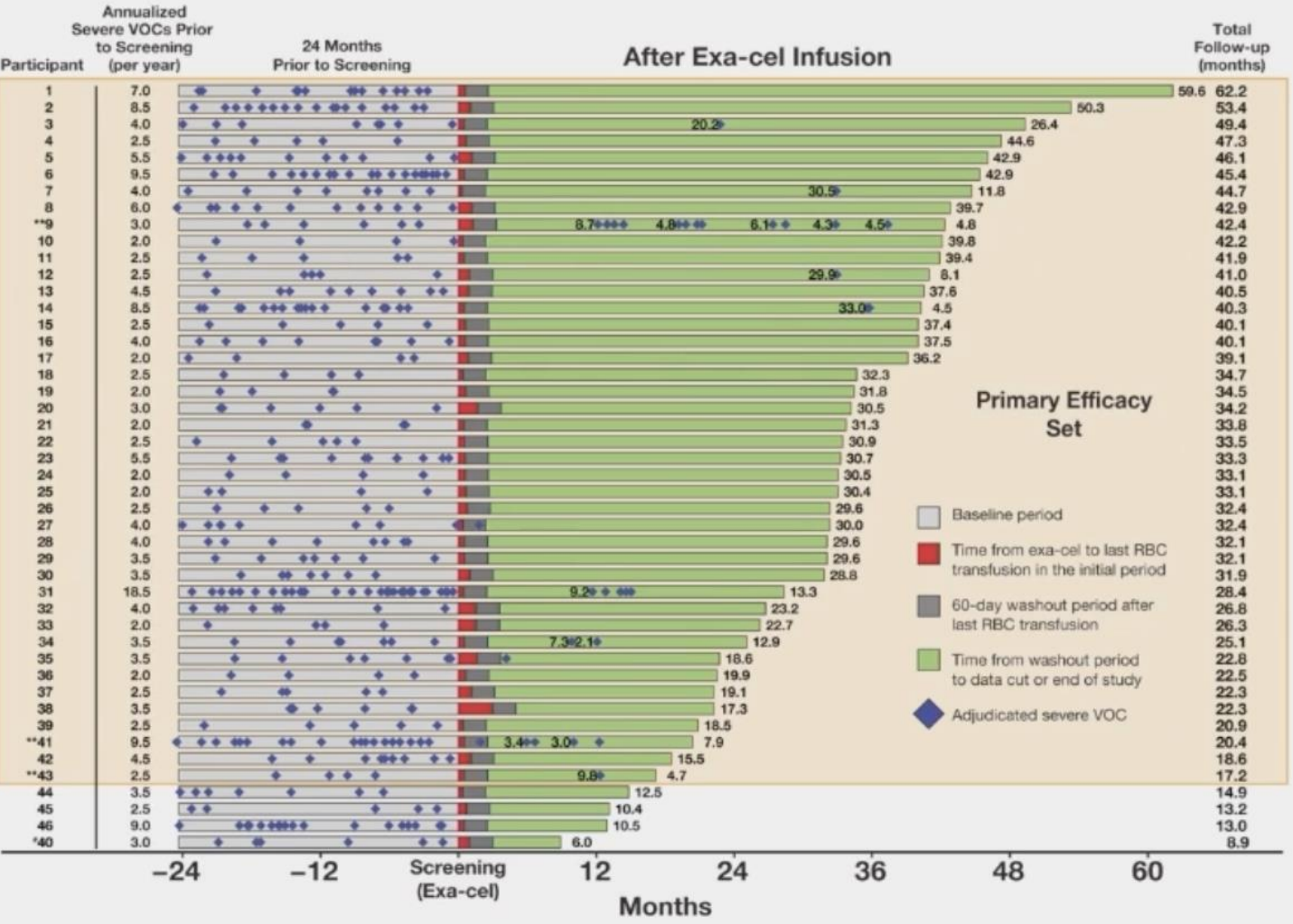
- 98% (53/54) of evaluable participants achieved TI12 in CLIMB THAL-111 and CLIMB-131 (95% CI: 90%, 100%)
- Mean duration of transfusion independence *34.5 months (range 15.0 to 64.1)*
- 1 participant who has not yet achieved TI12 has been transfusion free for the last 8.2 months

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.

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

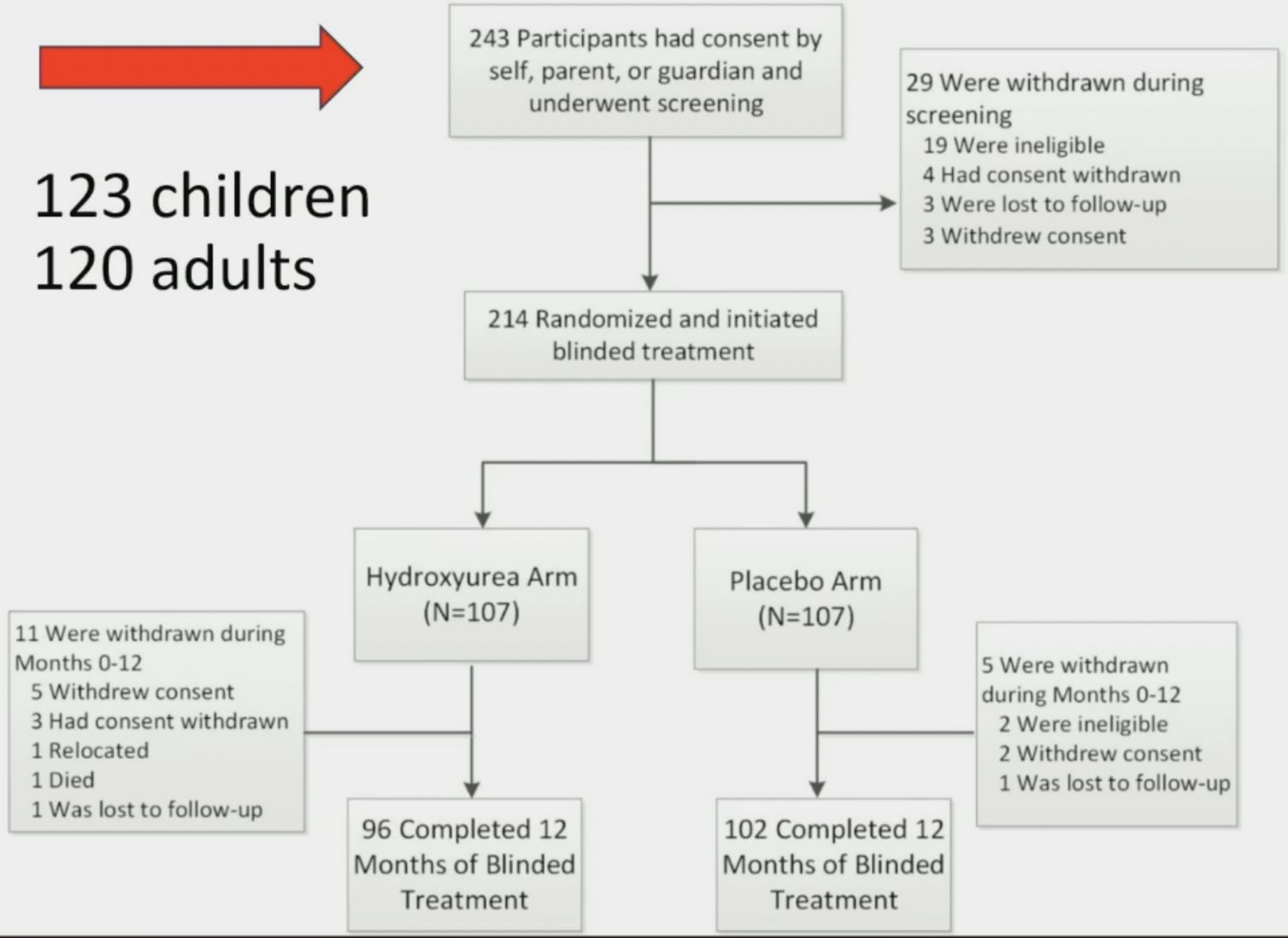
Cincinnati Children's
changing the outcome together

theravia

# 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 | - |

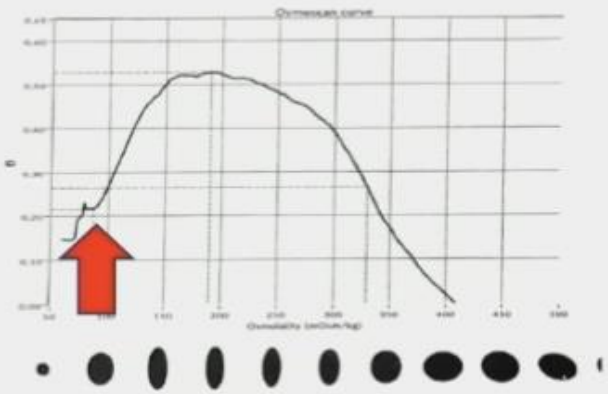
# Clinical Adverse Events (per 100 person-years)

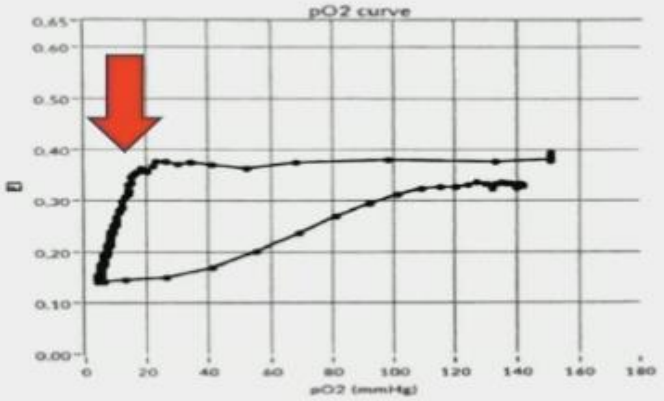
| | Hydroxyurea | | | Placebo | | | IRR (95% CI) |
|---|---|---|---|---|---|---|---|
| | Pediatric N = 56 | Adult N = 51 | All N = 107 | Pediatric N = 56 | Adult N = 49 | All N = 105 | All |
| **All Clinical AE** | 284.6 | 218.1 | 253.8 | 358.1 | 340.2 | 349.8 | 0.70 (0.48-0.92) |
| **Vaso-occlusive 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

**Sophia Delicou**,[1] Fuad El Rassi,[2] Biree Andemariam,[3] Miguel R. Abboud,[4] Julie Kanter,[5] Marilyn J. Telen,[6] Jessie Githanga,[7] Adlette Inati,[8] Ibrahim Idris,[9] Sunil Navani,[10] Eric Wu,[11] Andrew Eisenberger,[12]

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

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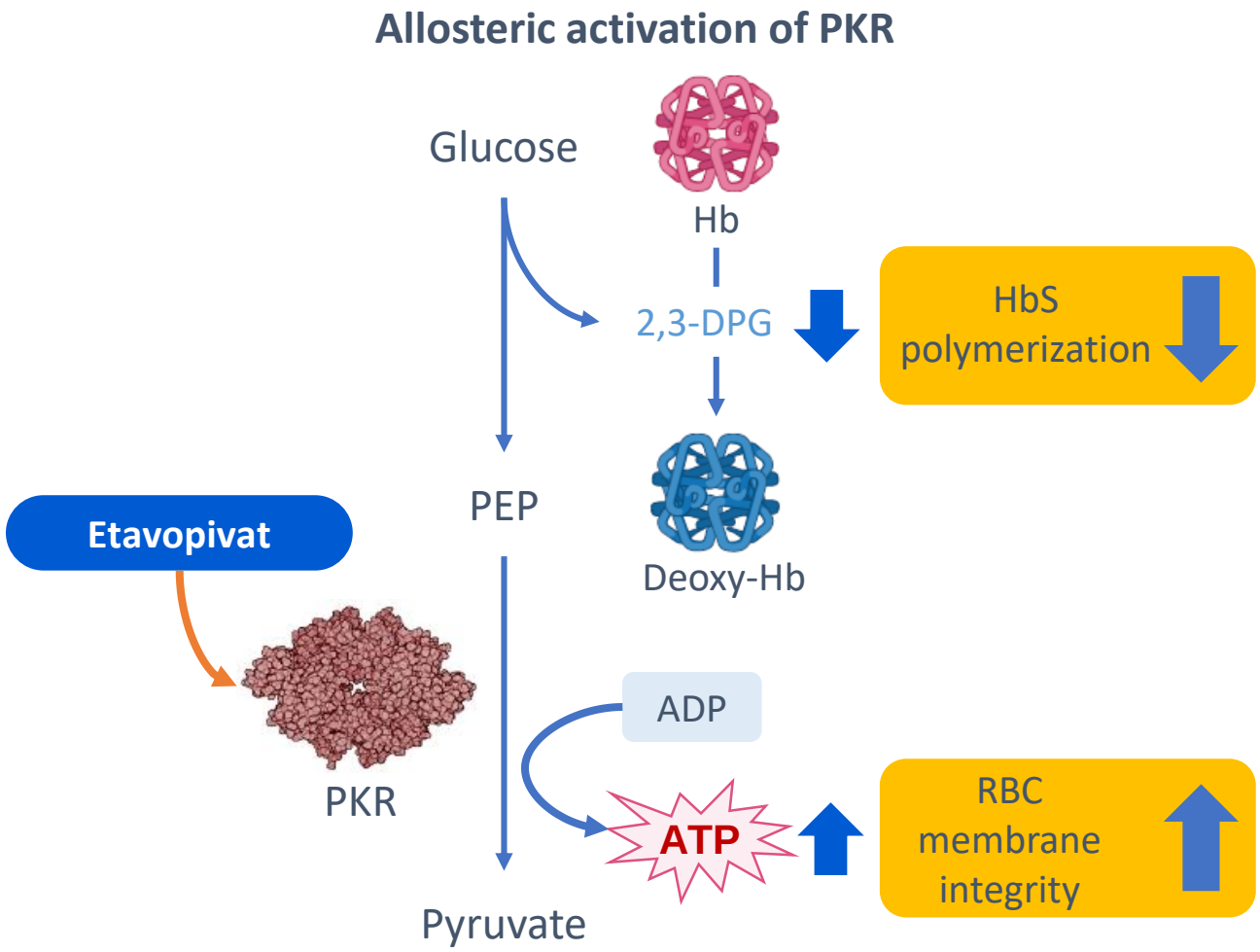
# Etavopivat: multimodal mechanism of action




- 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]

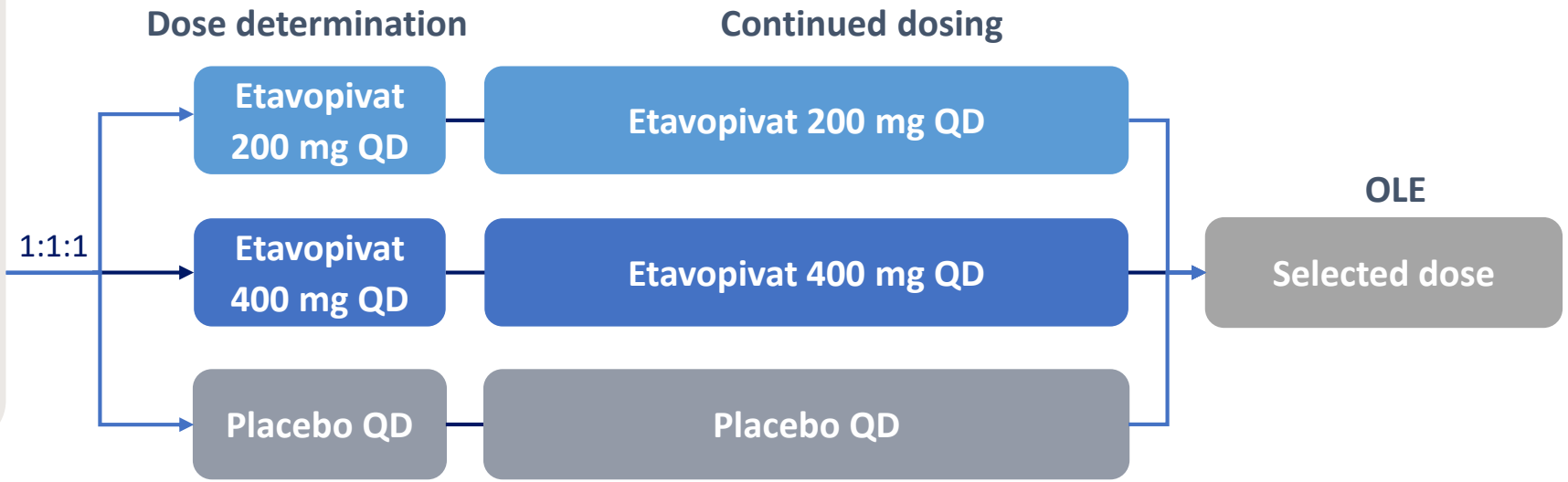
ADP, adenosine diphosphate; ATP, adenosine triphosphate; DPG, diphosphoglycerate; Hb, hemoglobin; HbS, sickle hemoglobin; PEP, phosphoenolpyruvate; PKR, RBC pyruvate kinase isozyme; RBC, red blood cell; SCD, sickle cell disease.

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

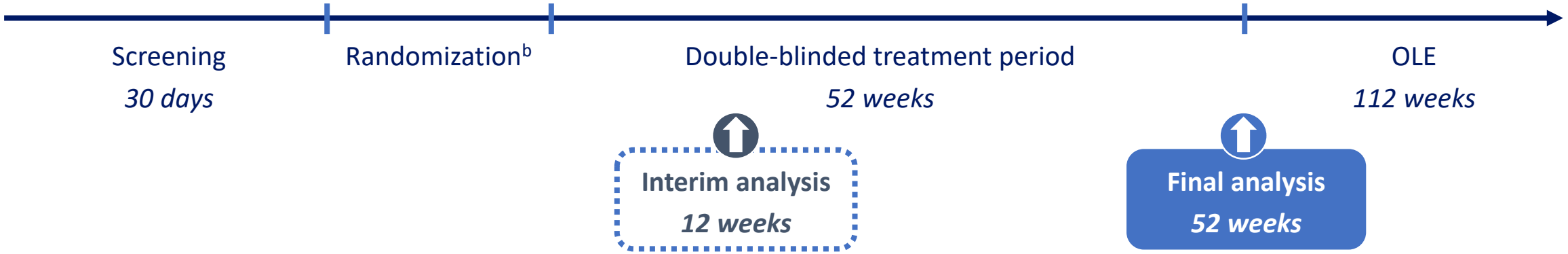
# HIBISCUS: Phase 2 dose determination study design

**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*

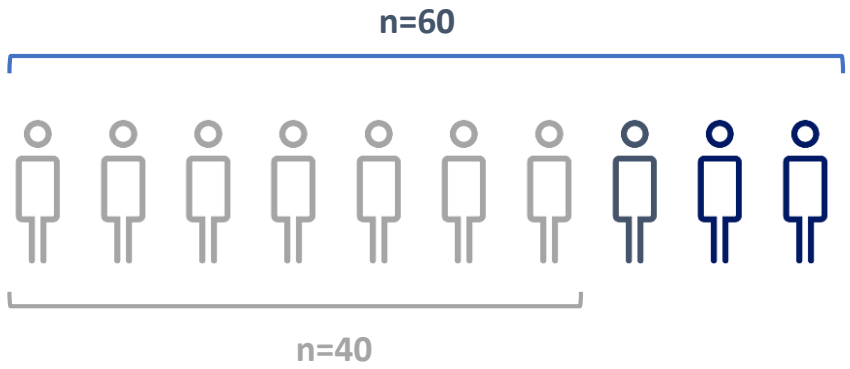
- Change from baseline in hemolysis biomarkers (absolute reticulocyte count, indirect bilirubin, and lactate dehydrogenase) at Week 24
- Change from baseline in Hb at Week 52 during the blinded treatment period
- Time to first VOC
- Change from baseline in PROMIS Fatigue Scale score[c] at Week 52

## *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.

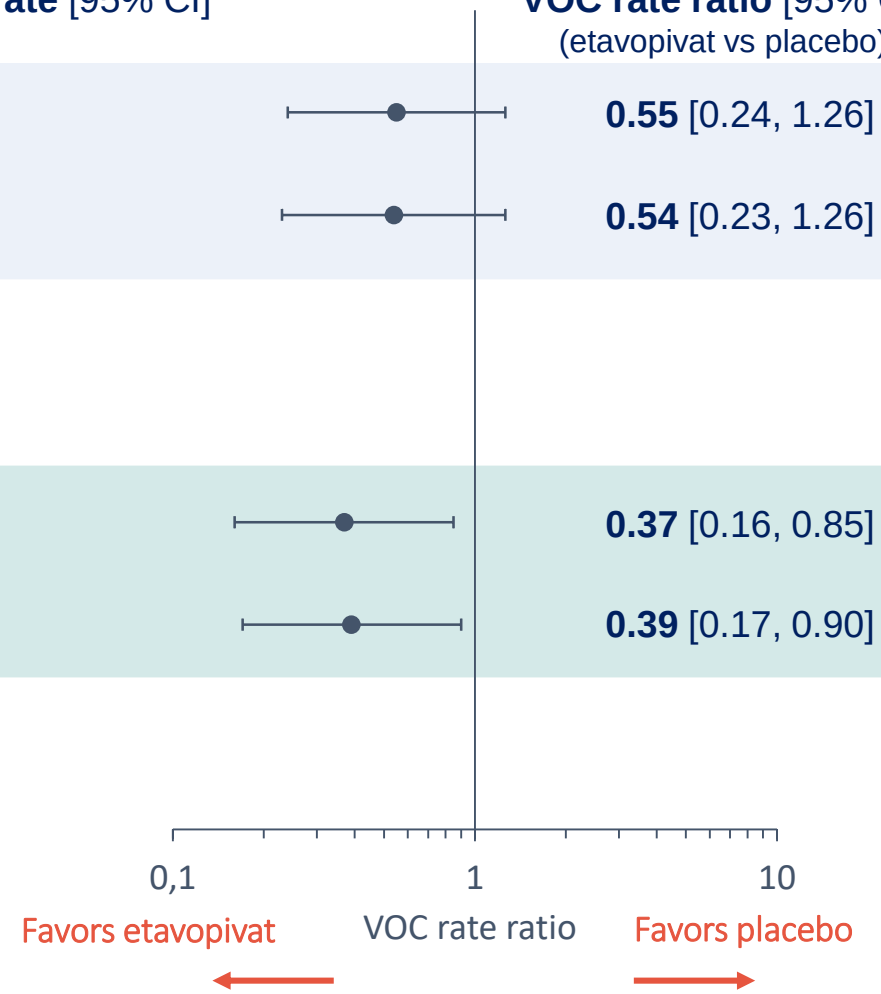
# **HIBISCUS:** Demographics and baseline characteristics

| | 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-$\beta^+$ thalassemia, n (%) | 1 (4.8) | 0 | 0 |
| Hb S-$\beta^0$ 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.

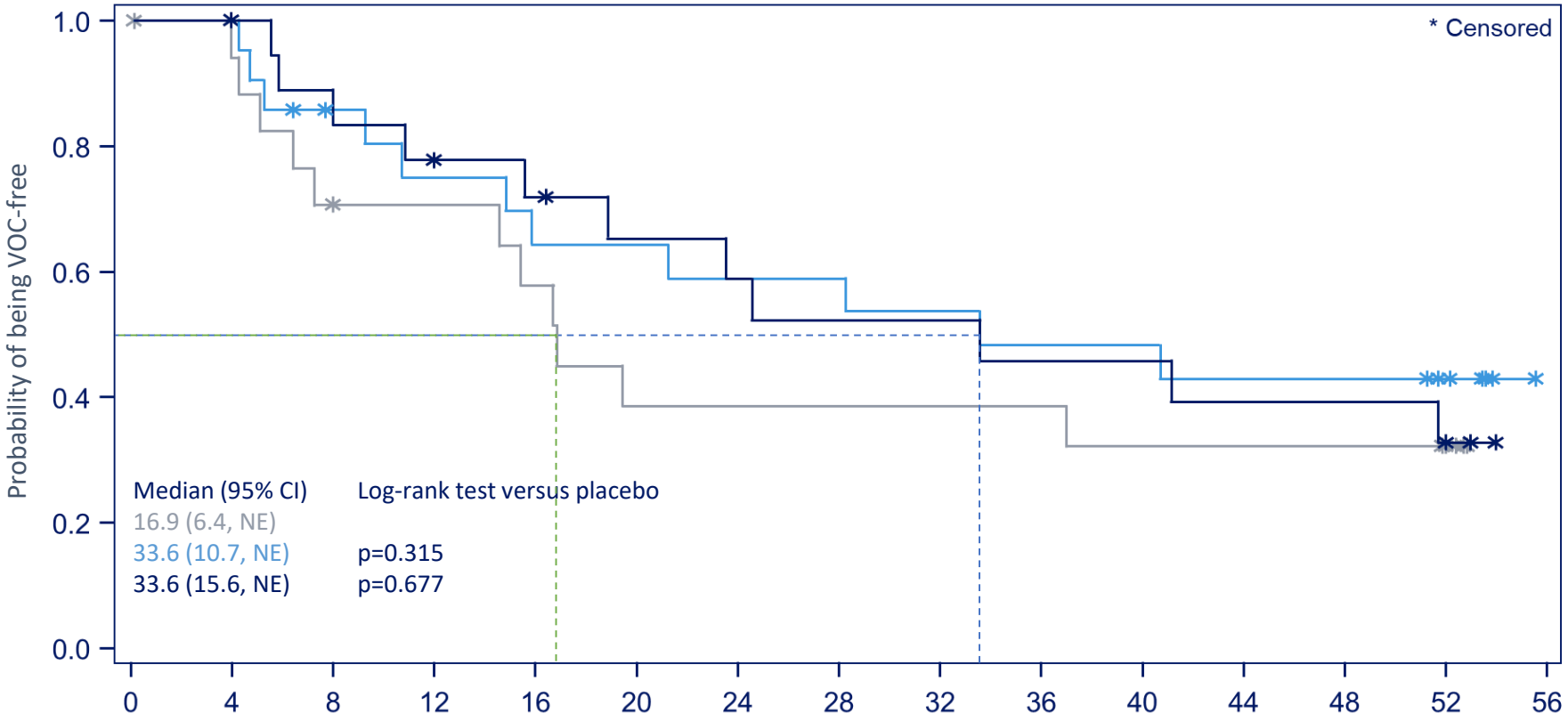
# **HIBISCUS:** Annualized adjudicated VOC rate

| | | **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

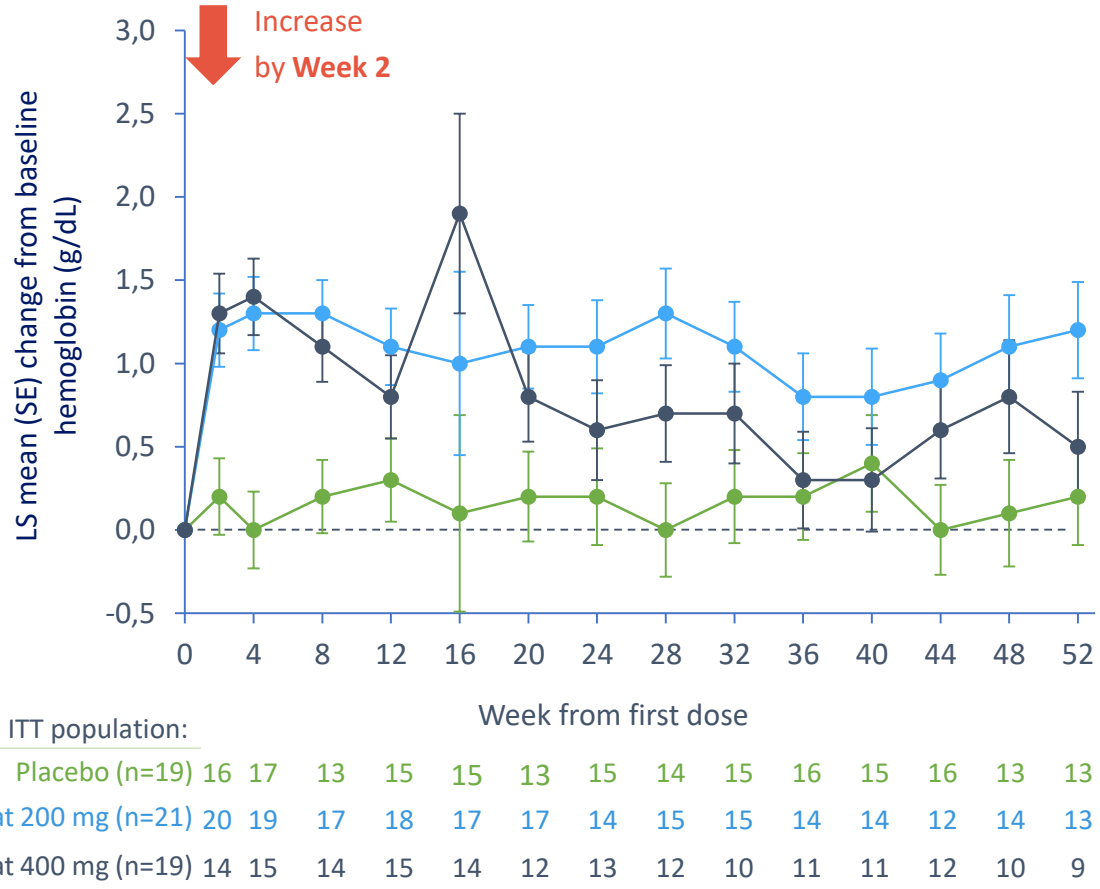



| ITT population: | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo (n=19) | 19 | 17 | 12 | 11 | 9 | 6 | 6 | 6 | 6 | 6 | 5 | 5 | 5 | 4 | 0 |
| Etavopivat 200 mg (n=21) | 21 | 21 | 16 | 14 | 12 | 12 | 11 | 11 | 10 | 9 | 9 | 8 | 8 | 6 | 0 |
| Etavopivat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

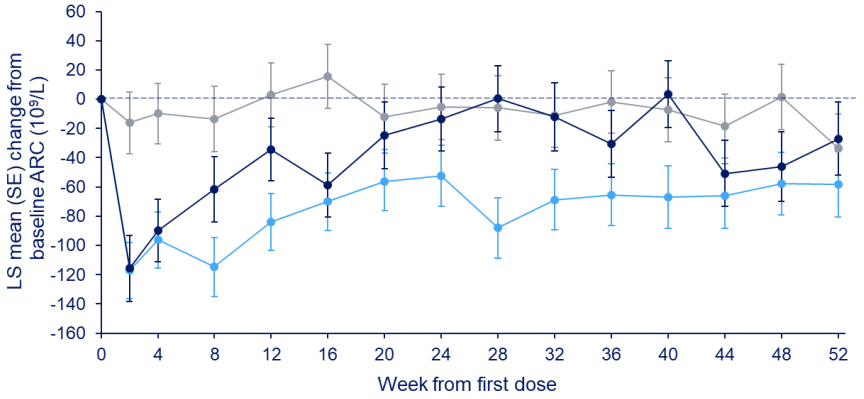
| | Etavopivat 200 mg/day | Etavopivat 400 mg/day | Placebo |
|---|---|---|---|
| ITT population | n=21 | n=20 | n=19 |
| **Hb responders at Week 24, %** | **38.1** | **25.0** | **10.5** |
| Rate difference vs placebo | 27.6 | 14.5 | |
| p-value | p=0.187 | p=0.660 | |
| PP population | n=13 | n=12 |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




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.

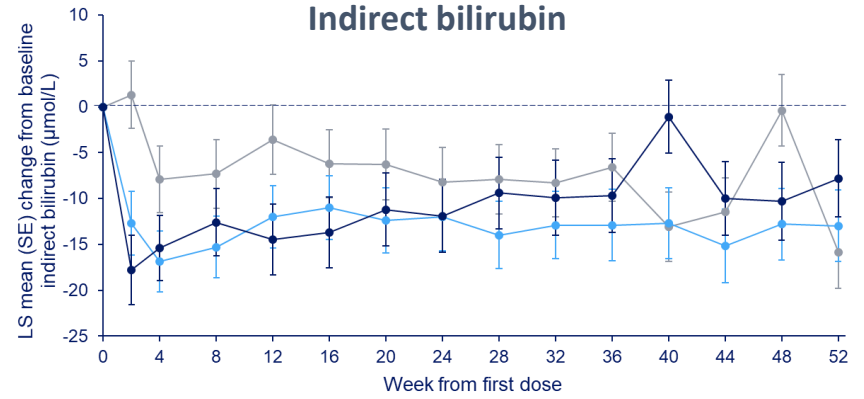
# **HIBISCUS:** Changes in markers of hemolysis

## Absolute reticulocyte count



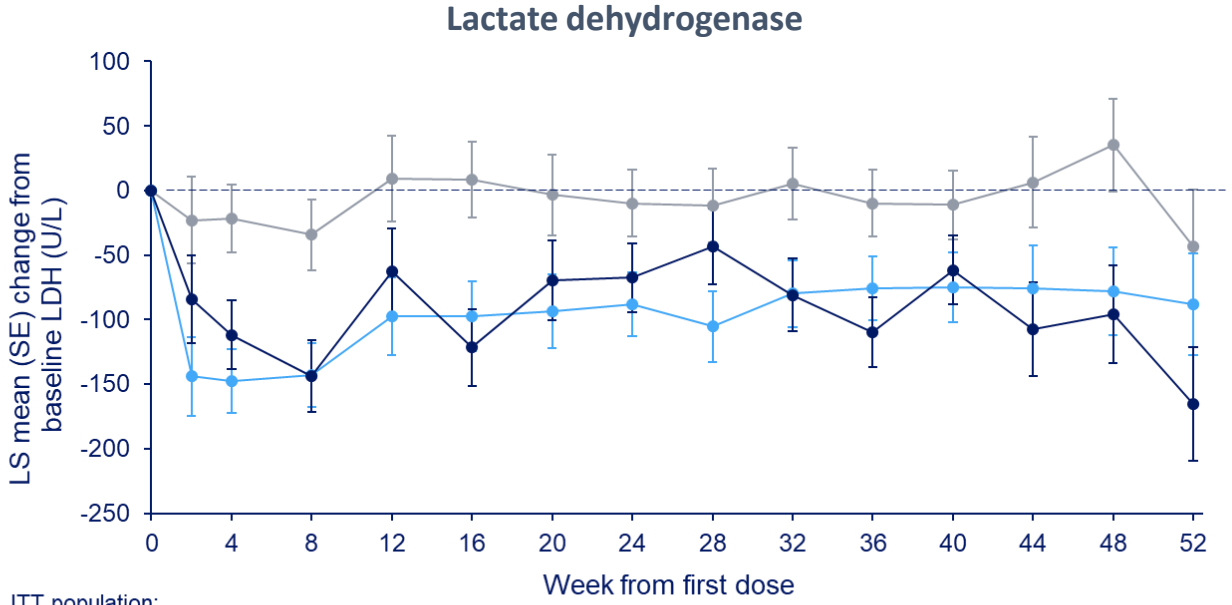

| ITT population: | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo (n=18) | 14 | 16 | 12 | 13 | 13 | 12 | 12 | 13 | 12 | 15 | 13 | 14 | 12 | 11 |
| Etavopivat 200 mg (n=20) | 19 | 18 | 15 | 18 | 17 | 17 | 13 | 14 | 15 | 14 | 14 | 12 | 14 | 12 |
| Etavopivat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

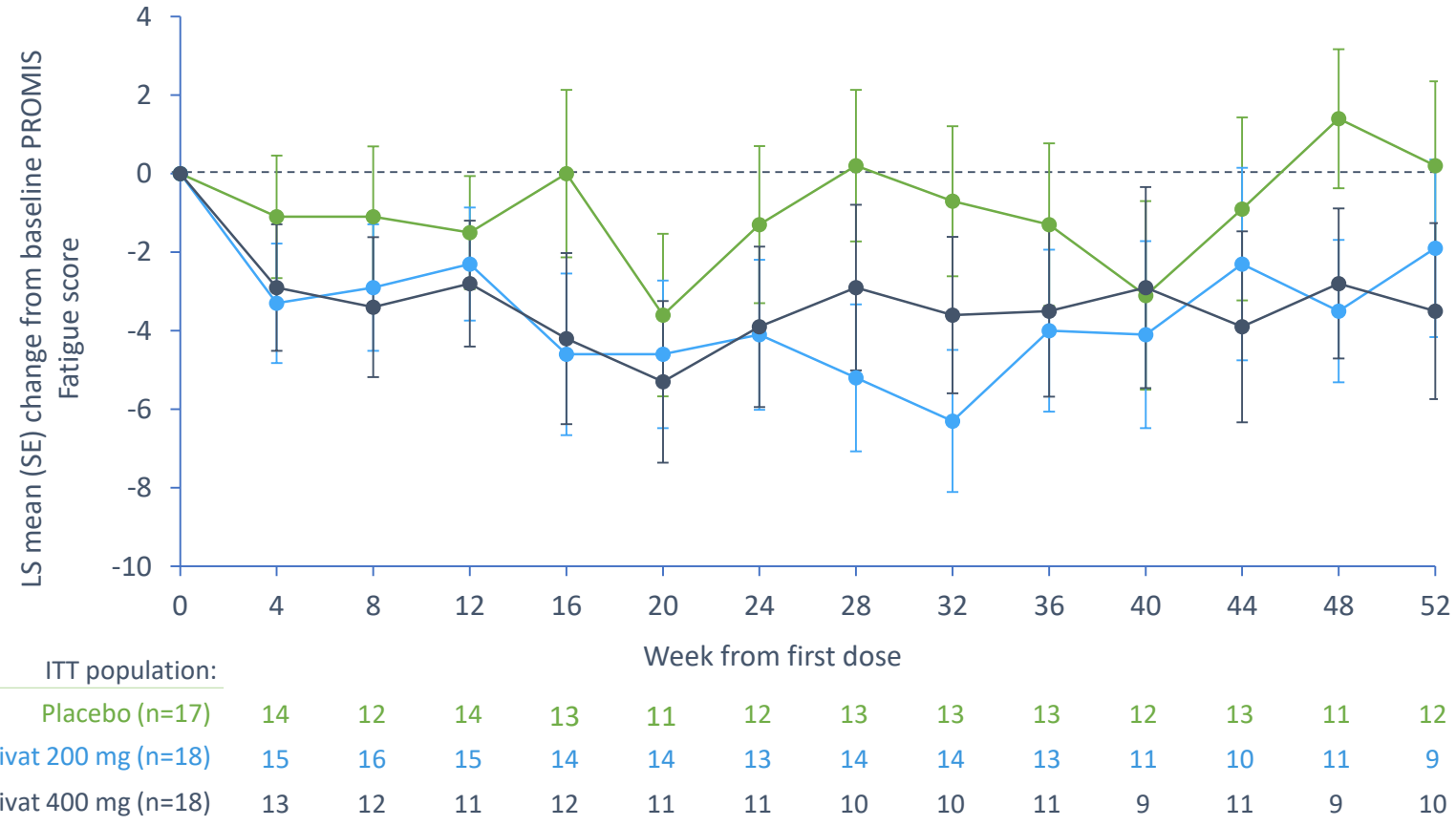
## Lactate dehydrogenase




| 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.

# Merci !

# Back up slides

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

# Novità dal Meeting della Società Americana di Ematologia

Bologna
Palazzo Re Enzo
13-15 Febbraio 2025

COORDINATORI
Angelo Michele Carella
Pier Luigi Zinzani

BOARD SCIENTIFICO
Paolo Corradini
Mauro Krampera
Fabrizio Pane
Adriano Venditti

Name Surname

**Title**

*Affiliation*

# Exa-cel Pivotal Phase 3 Program in Patients with TDT and SCD

| | TDT: CLIMB THAL-111 (NCT03655678) | SCD: CLIMB SCD-121 (NCT03745287) |
|---|---|---|
| **Study Design** | Global, multicenter, open-label, single-arm, 2-year Phase 1/2/3 trial of a single infusion of exa-cel | |
| **Participants** | 12 to 35 years of age with TDT defined as a history of ≥100 mL/kg/year or ≥10 units/year of RBC transfusions in the previous 2 years | 12 to 35 years of age with severe SCD and a history of ≥2 severe VOCs per year in the previous 2 years |
| **Primary and Key Secondary Efficacy Endpoint** | **Primary**: Proportion of participants **transfusion independent for ≥12 consecutive months** while maintaining a weighted average hemoglobin ≥9 g/dL **(TI12)** | **Primary:** Proportion of participants **free of severe VOCs for ≥12 consecutive months (VF12)**<br><br>**Key Secondary:** Proportion of participants **free from in-patient hospitalization for severe VOCs for ≥12 consecutive months (HF12)** |
| **Secondary And Additional Efficacy Endpoints** | • **Duration transfusion independence for participants who achieved T112** | • **Duration of VOC freedom for participants who achieved VF12** |
| | • **Total Hb and HbF levels**<br>• **Allelic editing at the intended locus in bone marrow CD34+ HSCs and peripheral blood cells**<br>• **Patient-reported outcomes (PRO) measures** | |

## CLIMB 131 (NCT04208529)

Global, multicenter, open-label, rollover Phase 3 study to provide up to 15 years of long-term efficacy and safety follow-up

**Updated data from CLIMB THAL-111 and 131 demonstrates durable clinical benefit in TDT with the longest follow-up of ~5 years**

**Data from CLIMB SCD-121 and are being presented in POSTER #4954; also demonstrate durable clinical benefit in SCD**

# **HIBISCUS:** Concomitant disease-modifying therapies at randomization

| | Etavopivat 200 mg/day (n=21) | Etavopivat 400 mg/day (n=20) | Placebo (n=19) |
|---|---|---|---|
| **Prior year's use**, n (%) | | | |
| Hydroxyurea | 17 (81.0) | 13 (65.0) | 14 (73.7) |
| Voxelotor[a] | 2 (9.5) | 1 (5.0) | 1 (5.3) |
| Crizanlizumab | 2 (9.5) | 3 (15.0) | 2 (10.5) |
| L-glutamine | 0 | 0 | 2 (10.5) |
| Received RBC transfusion | 7 (33.3) | 6 (30.0) | 5 (26.3) |
| **On-trial use** of SCD therapies, n (%) | | | |
| Hydroxyurea | 16 (76.2) | 13 (65.0) | 14 (73.7) |
| Crizanlizumab | 1 (4.8) | 2 (10.0) | 1 (5.3) |
| L-glutamine | 0 | 0 | 1 (5.3) |

[a]Voxelotor was not permitted to be used within 28 days prior to starting the study treatment or anticipated need for this agent during the study.
RBC, red blood cell; SCD, sickle cell disease.