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Management of, and unmet needs in, Sickle Cell Disorders

Declaration of Interests

- Silence Therapeutics- scientific advisory board, research funding
- Agios- advisory board
- Bluebird Bio- advisory boards
- BMS- advisory boards
- Vifor- advisory boards

Outline

- Underlying mechanisms of SCD
- Clinical consequences
- Scale of the global challenge
- Therapeutic approaches to these mechanisms
  - Non-curative approaches
  - Curative approaches
- Unmet needs

Mechanisms and consequences of SCD

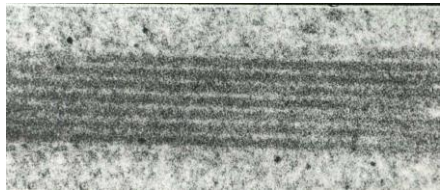
HbS β6 glu→val

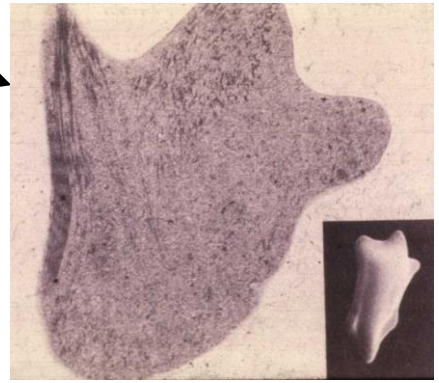
$(\alpha_2\beta^S_2)$

$+O_2$ ⇅ $-O_2$

Polymerization of deoxy HbS

Low O_2 tension





Red cell distortion

NO scavenging

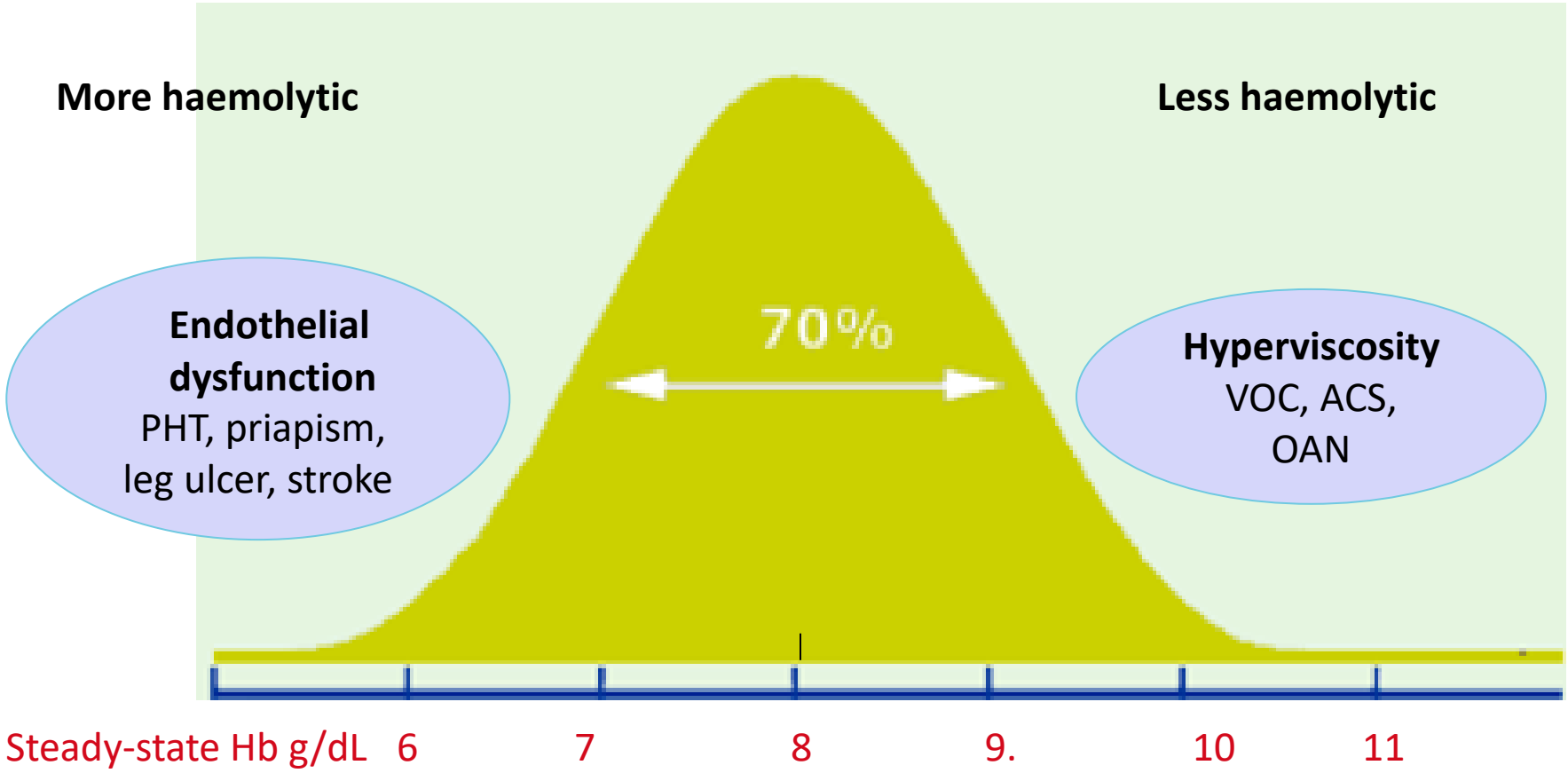
Hemolytic anaemia

Red cell endothelial interaction
Vaso-occlusion

Microvascular obstruction

- **Acute painful crises**
- **Chronic progressive organ damage**

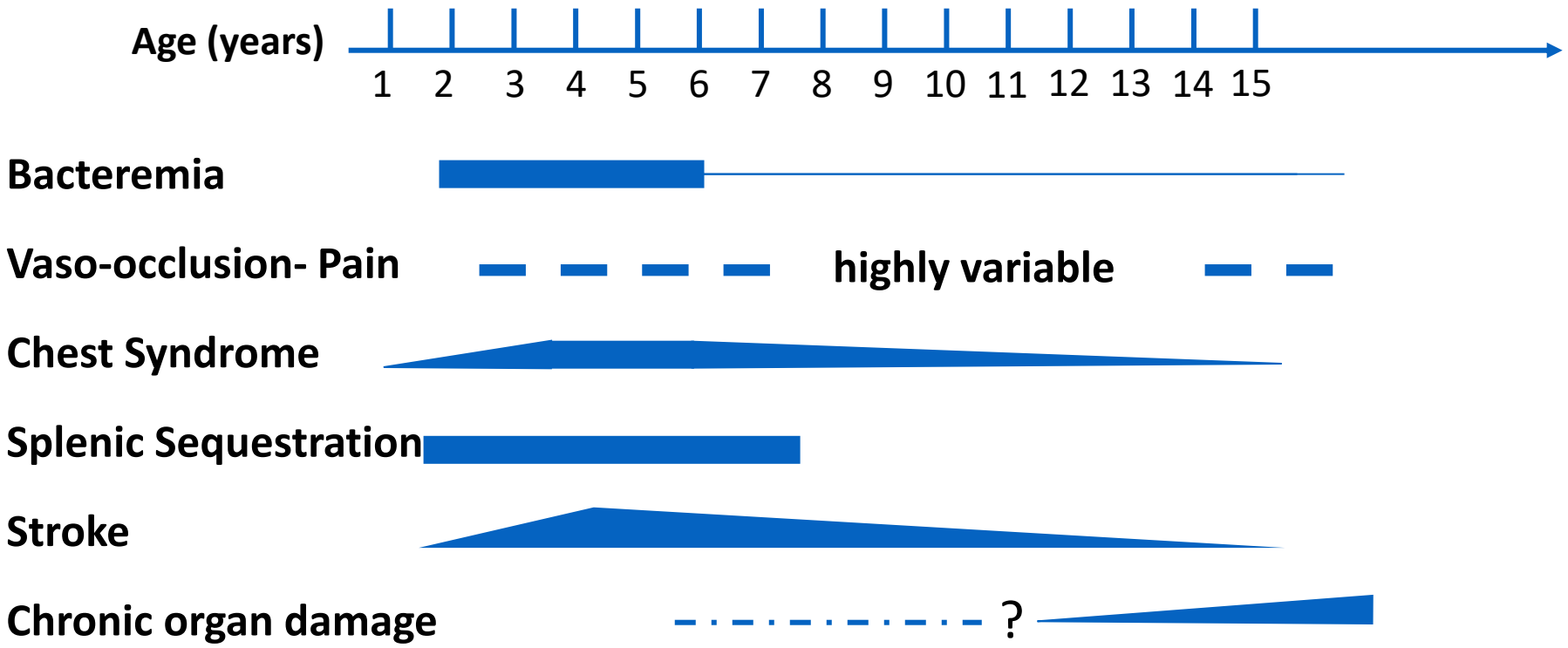
Range of Clinical Phenotypes of SCD according to steady-state Hb Level



ACS = acute chest syndrome; Hb = hemoglobin; PHT = pulmonary hypertension; VOC = vaso-occlusive crisis

Adapted from Kato GJ, et al. *Blood Rev*. 2007;21(1):37-47.

Complications of SCD in Children



Gill FM, et al. *Blood*. 1995;86(2):776-783. Ohene-Frempong K, et al. *Blood*. 1998;91(1):288-294. Castro O, et al. *Blood*. 1994;84(2):643-649.

Complications of SCD in Adults

Acute
Vaso-occlusive painful crises
Acute chest syndrome
Infections (hyposplenism) & Iron
Acute anaemia
Splenic sequestration
Parvovirus
Priapism
Stroke

Scale of the global challenge- births

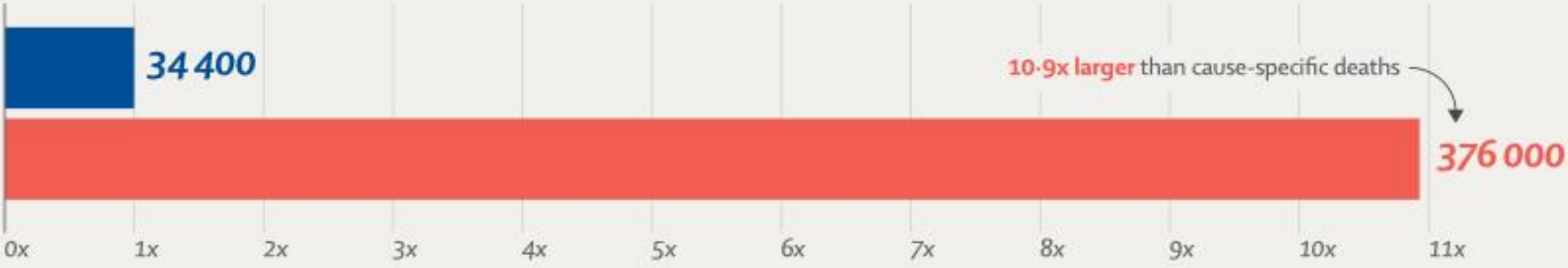
- **Commonest inherited disorder of humans**
- ***Historical distribution*** **- Reflects advantage of AS against malaria**
  (Subsaharan Africa, Middle East, India, Mediterranean)
- ***Contemporary distribution*** **- Reflects migration patterns**
- ***Carrier rates (AS)***
  - **Subsaharan Africa** **~20%**
  - **Afro-Caribbeans** **~13%**
  - **India** **~1-40 % patchy** (Verma, Colah. WHO 2008)
  - **USA** **~1% (3M out of 303M)**
  - **UK** **~1.6% (pregnant carriers)**
- ***Birth rates with SCD***
  - **Worldwide** **~ 300,000 births pa increasing to 404,000 by 2050** (Piel et al 2013)
  - **Subsaharan Africa** **~ 2% of births** (150k pa Nigeria, 160M population)
  - **Saudi Arabia** **~ 0.5% of births** (El-Hazmi et al, 1997)
  - **India** **~ 20,000 births pa** (Verma, 2008)
  - **UK** **~ 0.056 % of births** (NHS screening program)
    ~ 270 births pa

Scale of the SCD global challenge- deaths

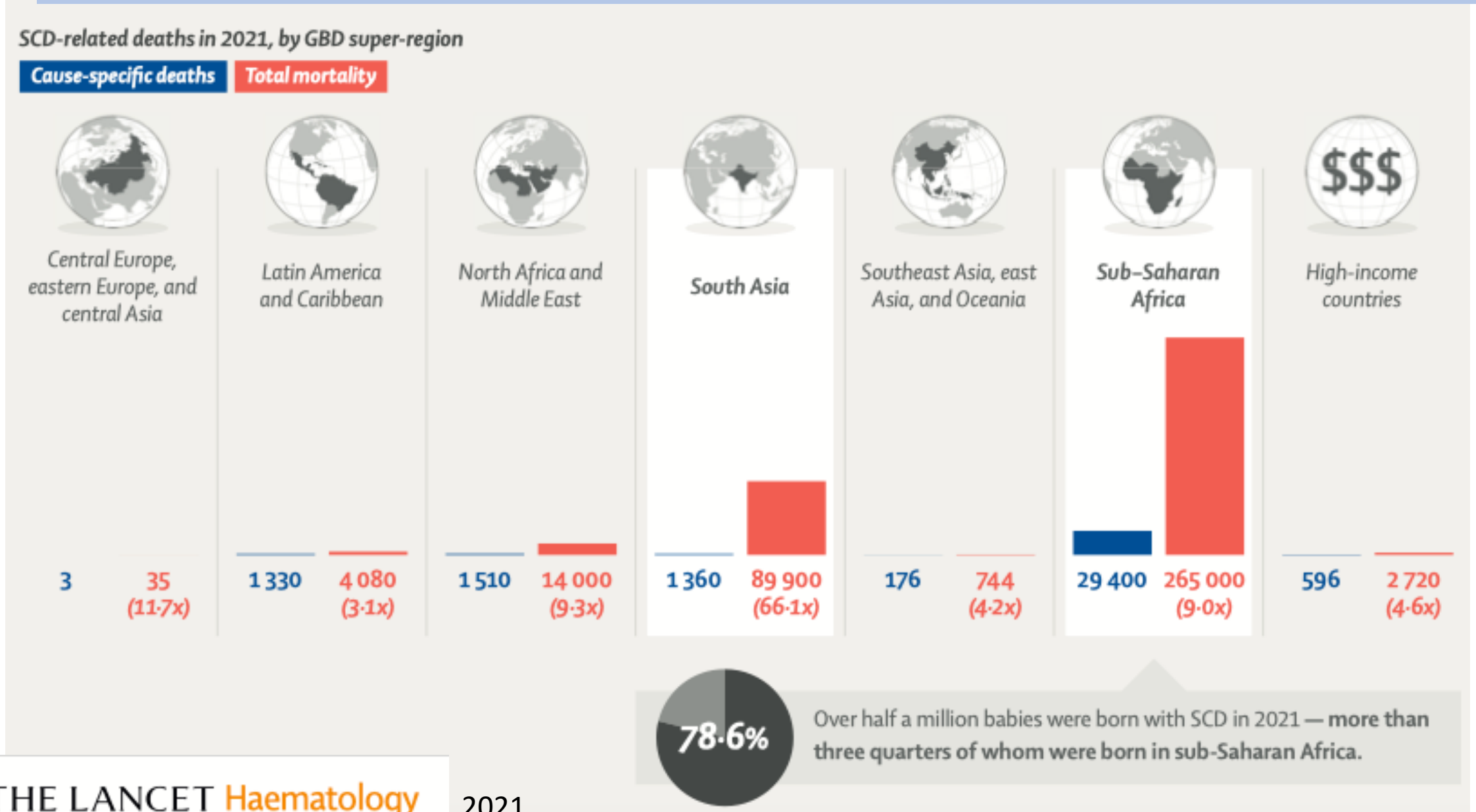
Sickle cell disease—global mortality burden is nearly 11 times higher than recorded

A *Lancet* study—the first to estimate the full global mortality burden of Sickle Cell Disease (SCD)—has revealed a strikingly high contribution of SCD to all-cause mortality that is not apparent when each death is assigned to only a single cause.

THE LANCET Haematology 2021



Subsaharan Africa and South Asia bear the brunt of the mortality burden in SCD



THE LANCET Haematology 2021

Management strategies: Prevention, Care, Modification or Cure?

- **Screening and education of at-risk couples**
  - Newborn screening
  - Counselling - Prenatal + Premarital
  - Maternal carrier testing
  - Prenatal diagnosis
- **Prevent and treat acute complications**
  - Train doctors, nurses and patients to:
  - Prevent and treat infections (esp. pneumococcal)
  - Prevent painful crises –education of patients and parents about risks
  - Recognize complications early (chest syndrome)
  - Educate about splenic sequestration especially
  - Treat pain rapidly and effectively
  - Stroke primary and secondary prevention
- **Prevent long term organ damage**
  - Stroke & Cognitive loss
  - Renal disease
  - Pulmonary hypertension
- **Specific anti-sickling options**
  - Transfusion
  - Hydroxyurea
  - New medications
- **Curative**
  - Stem cell transplantation
  - Gene Therapy

Therapeutic approaches mechanistically

↓HbS &↑HbA
- Blood transfusion
- Allogeneic HSCT
- Gene addition
  e.g. - lentiglobin BBB

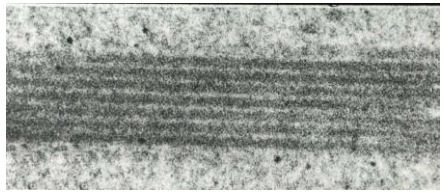
↓Hb polymerisation rate
- Increase Hb F %
  - Hydroxyurea)
  - Gene therapy BCL11A
- Modify Hb -increase O2 binding
  Voxelator

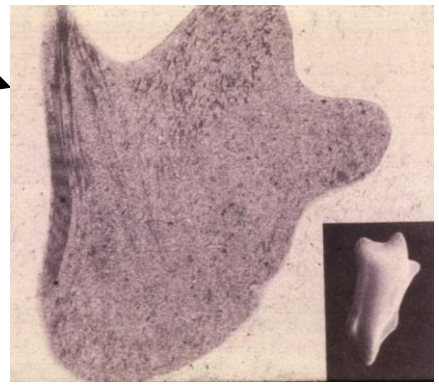
HbS β6 glu→val
$(\alpha_2\beta^S_2)$

$+O_2$ ↑ ↓ $-O_2$

Polymerization of deoxy HbS

Low O_2 tension





Red cell distortion

NO scavenging

↓ Hemolytic anaemia

↑ Red cell energy (ATP)
e.g. mitapivat

↑ Or O2 affinity
e.g. (voxelatpr)

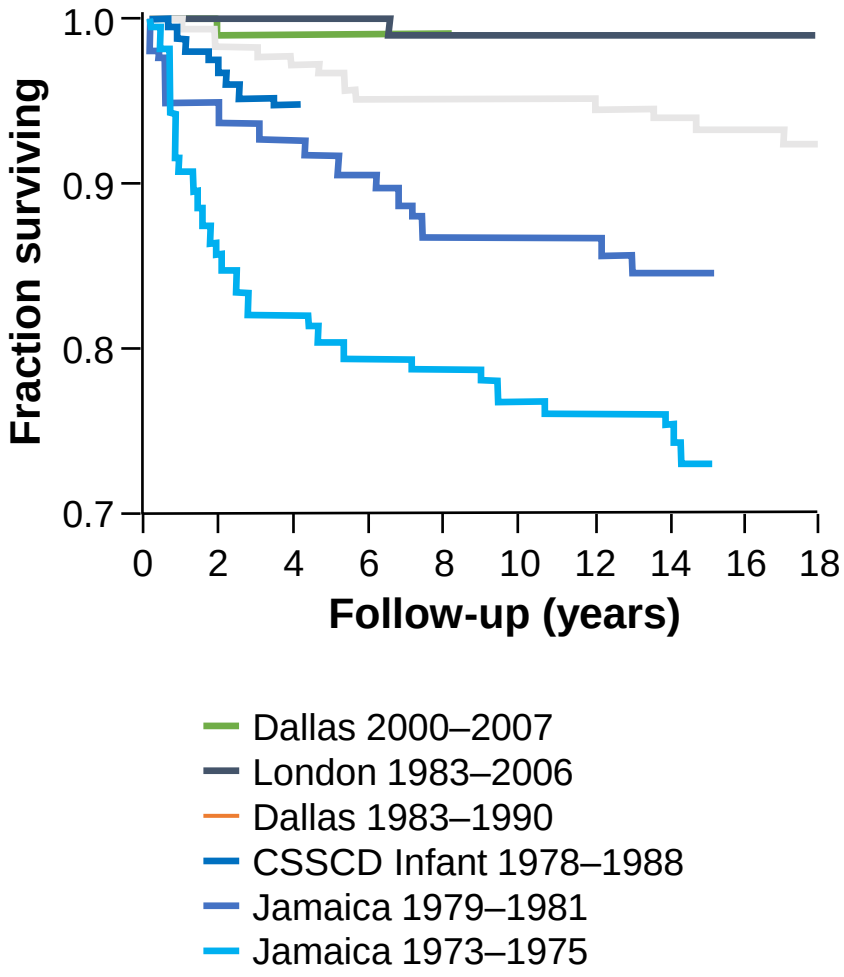
↓ Red cell endothelial interaction
Vaso-occlusion

Microvascular obstruction
- **Acute painful crises**
- **Chronic progressive organ damage**

- P Selectin anagtonists
  e.g *Crisanlusimab*
- Complement inhibition

Survival in paediatric patients has significantly improved

- Why ?
  - Vaccinations
  - Antibiotics
  - TCD monitoring
  - Transfusions
  - Neonatal screening
  - Comprehensive care

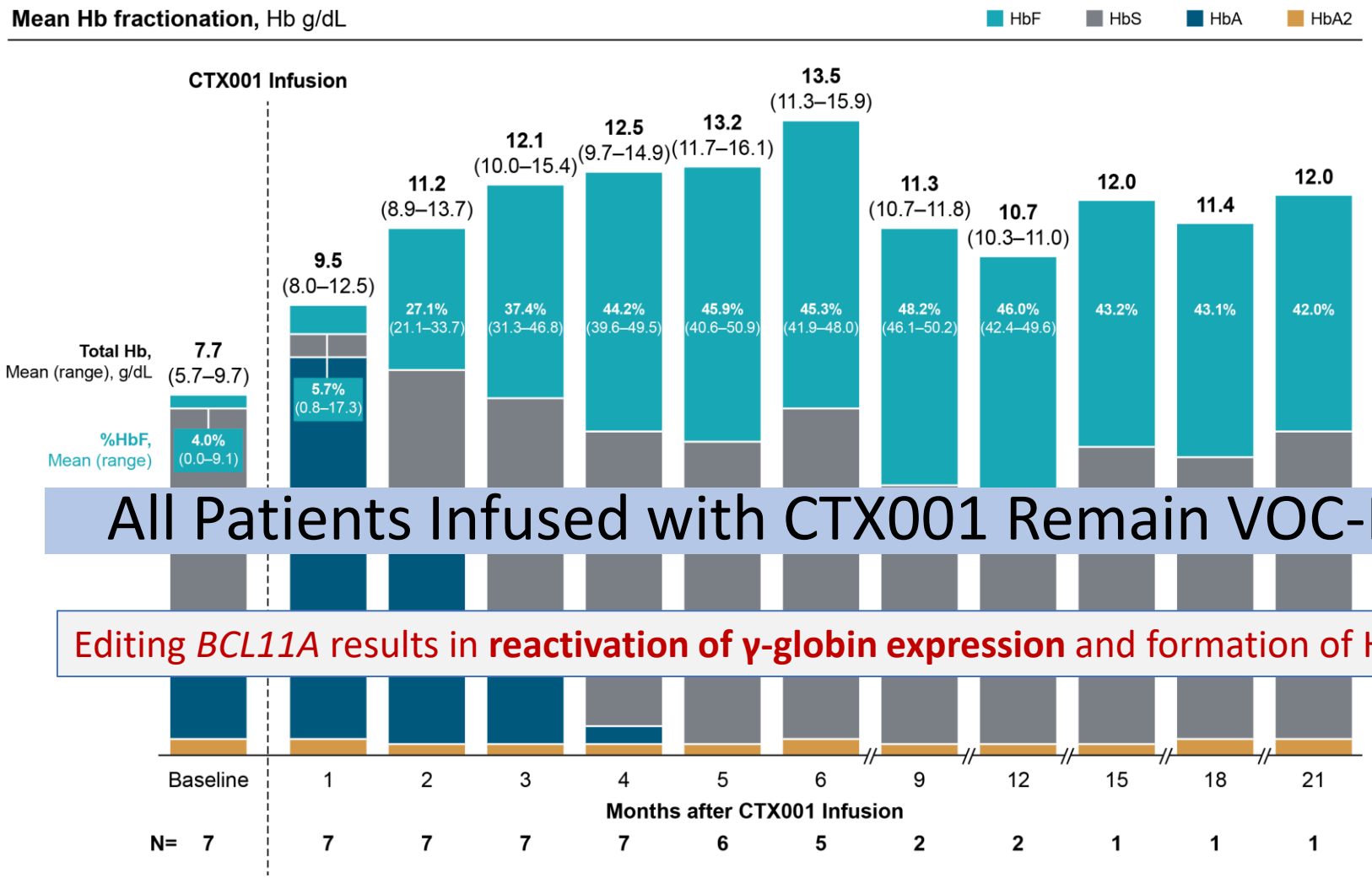


Overall survival at 18 years of age
- 93.9% HbSS/HbSβ^0
- 98.4% HbSC/HbSβ$^+$

TCD = transcranial Doppler.

Quinn CT, et al. Blood. 2010;115:3447-52.

Sickle cell patients demonstrated Increased Total Hb and HbF



- Increases in total Hb and HbF occurred early and were maintained over time; mean %HbF increased to >30% by 3 months following

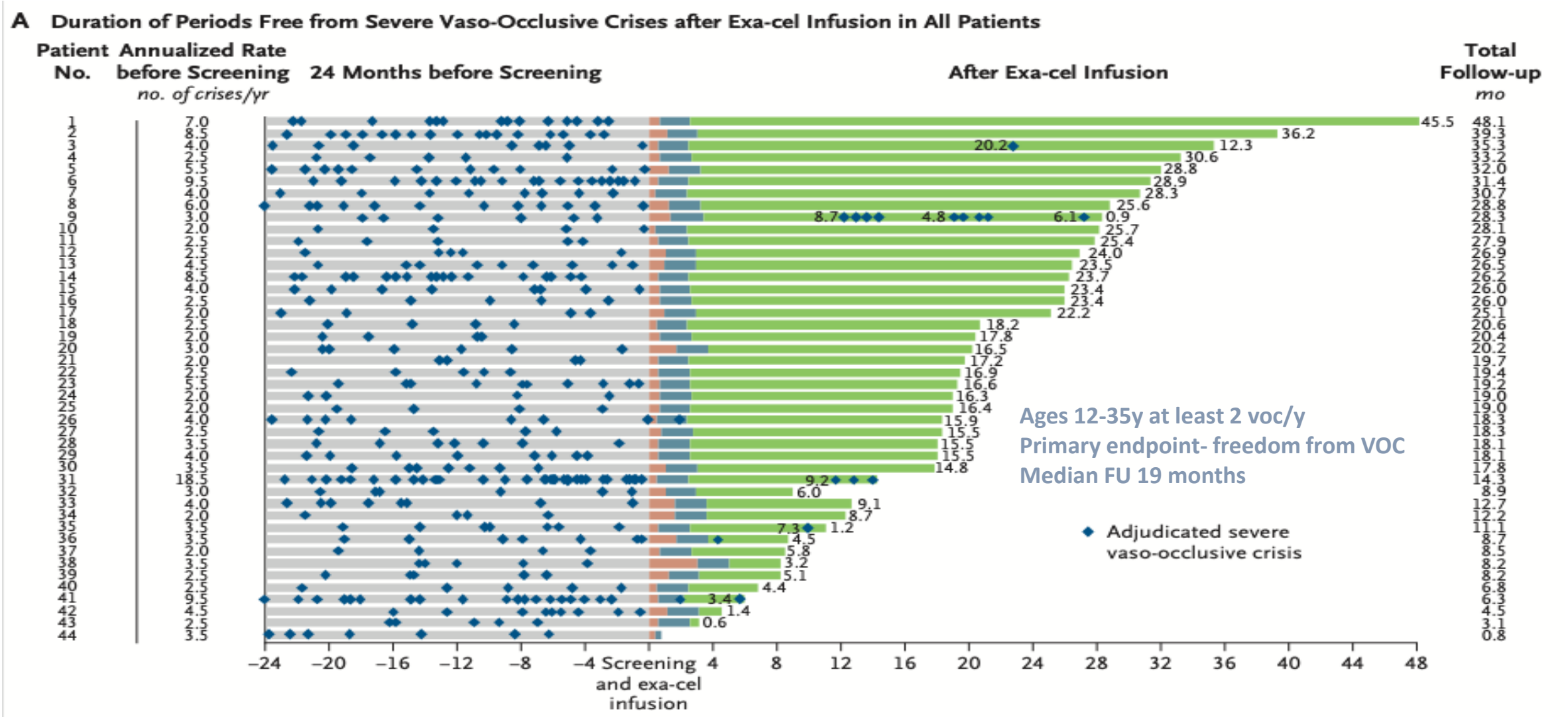
All Patients Infused with CTX001 Remain VOC-Free

Editing *BCL11A* results in **reactivation of γ-globin expression** and formation of HbF (α2γ2) i

CTX001™ for Sickle Cell Disease: Safety and Efficacy Results from the Ongoing CLIMB SCD-121 Study of Autologous CRISPR-Cas9-Modified CD34⁺ Hematopoietic Stem and Progenitor Cells. European Hematology Association, June 9 - 17, 2021

Exagamglogene Autotemcel for Severe Sickle Cell Disease

HSPCs edited with the use of CRISPR-Cas9



Frangoul et al, N Engl J Med. 390:1649-1662. May 2024;

Unmet needs 1- Scientific

- ***Improve non-curative therapies***
  - To improve impact of morbidity and mortality ?
    - New molecules / agents
      e.g. will the combined use of modalities have additive benefit ?
- ***Improving curative therapies***
  - HSCT (stem cell transplant)
    - Extending the range of potential donors
      - Extending the use and safety of haploidentical transplants
    - Conditioning regimens that do no involve myeloablative chemotherapy
    - Conditioning regimens that avoid infertility
  - Gene therapies
    - Conditioning without myeloablation
    - Without effects on fertility
    - Without procedure related morbidity/mortality
    - Cost

Unmet needs 2- Organisational

- Wider application of prevention programs
- Training and motivating of staff
  - Education of haematologists is dominated by oncologists
  - Chronic genetic disease is unattractive to many trainees
  - Education needs to increase exposure of all young doctors and nurse specialists to sickle disorders
  - Need to make attractive intellectually and financially to trainees
  - Stakeholder panels for case discussion & policy decisions
- Infrastructure/funding – how do health systems cope with ?
  - Increasing demand numerically from HbSS patients
  - Increasing number and cost of new treatments

Thank you