POST-ORLANDO 2025
Novità dal Meeting della Società Americana di Ematologia

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Torino
Centro Congressi Lingotto
19-21 febbraio 2026

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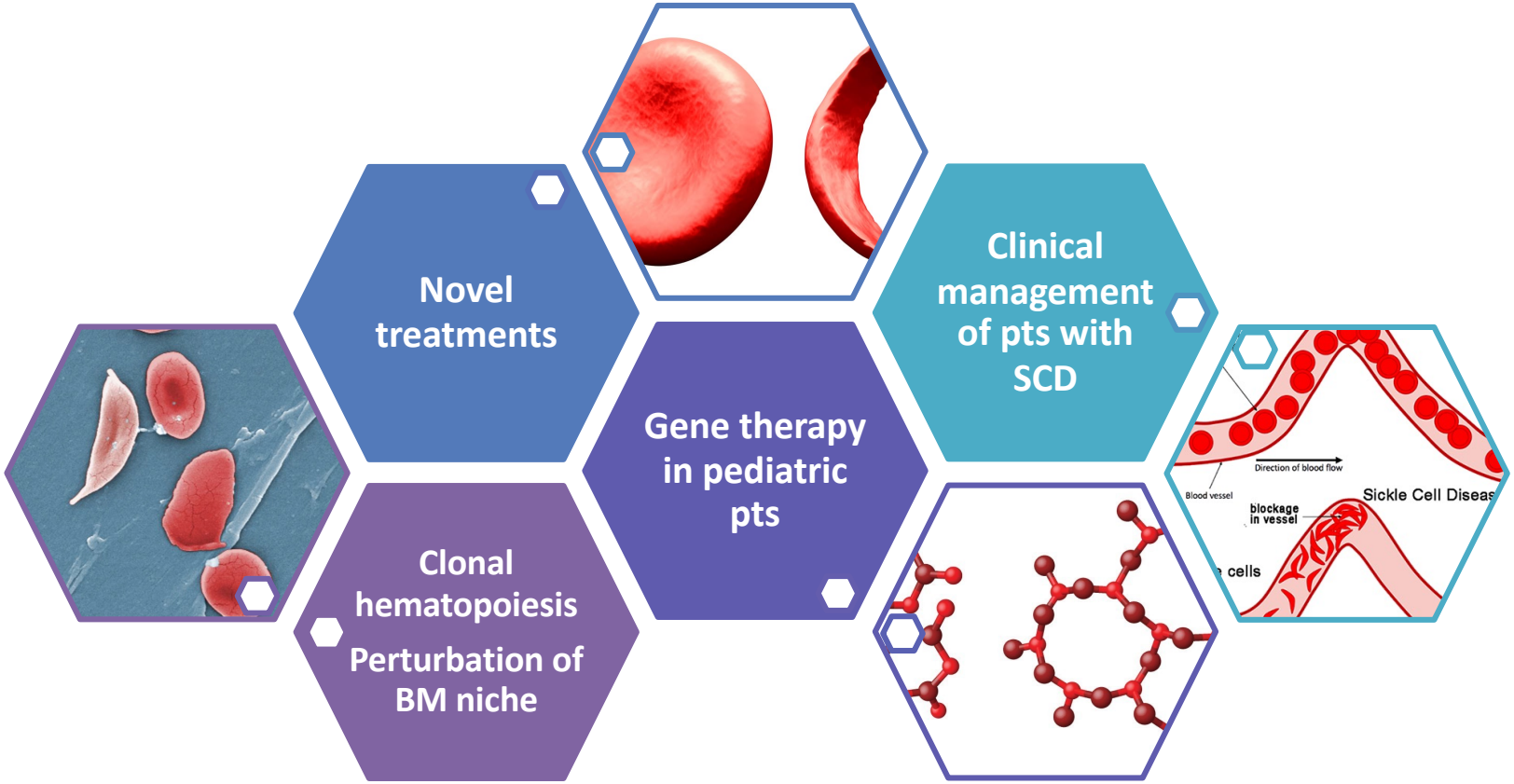


Higher HbF Levels Result in Reduced Symptomology in People Living With Sickle Cell Disease

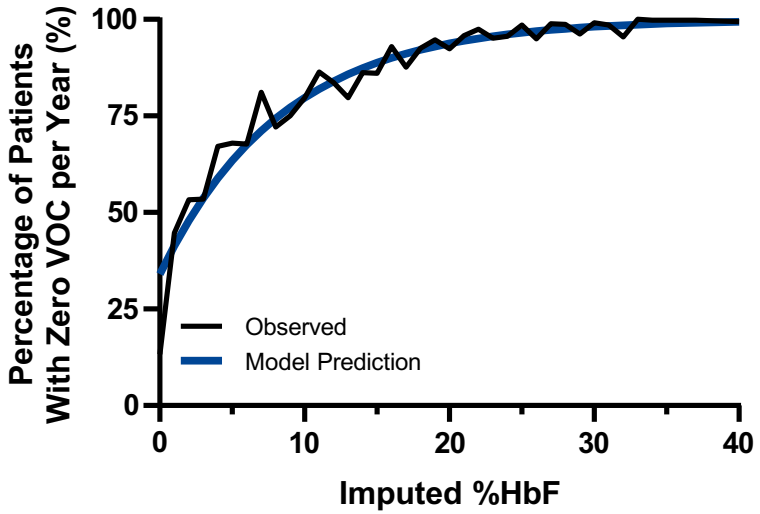
Each 1% increase in %HbF…

…is associated with a 4%–8% reduction in VOCs[1]

Raising HbF levels also results in:

- Reduced hemolysis
- Reduced anemia
- Fewer recurring events

Probability of Observing Zero VOC/Year by %HbF[2]



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HbF level	% of Patients reporting zero VOCs *(Model Prediction)*
15%	89%
20%	94%
25%	97%

HbF, fetal hemoglobin; VOC, vaso-occlusive crisis.
Peter Bruun-Rasmussen. ASH 2024 (poster 1124#.; Alan et al., 20th Annual Sickle Cell & Thalassaemia Conference. Br J Haematol, 207: S5-S135. 2025

Modified from M. Steimberg

Panobinostat, a Pan-Histone Deacetylase Inhibitor in Patients with SCD

- Panobinostat (PAN) inhibits HDAC isoforms at low concentration, improving HbF synthesis in 3 SCD patients treated for lymphoma

- **Phase I clinical trial (NCT 01245179) in adult patients with SCD not tolerating HU (age >18 years).**

- **Eligible population:**
  - SS, $S\beta^0$ genotypes
  - Severe phenotype:
    - 2 hospitalization for severe VOCs

    or
    - 3ED/outpatient treated VOCs in the previous year
    - ACS in the previous 5 years
    - Recurrent leg ulcers
    - History of priapism

Pace SB et al. BJH 194: 240, 2021;
Kutlar A Blood 146: 613, 2025

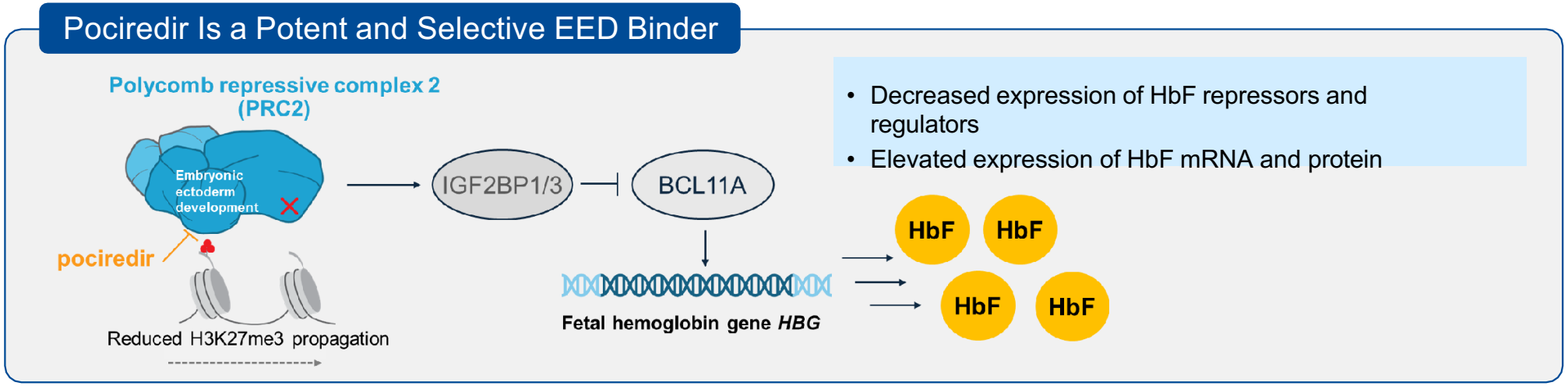
Panobinostat increases HbF expression and F-cells in adult patients with SCD

- **Panobinostat:**
  - 15 mg/d PO for Monday/Wednesday/Friday for 12 weeks (**cohort 1, n=3**)
  - 20 mg/d PO for Monday/Wednesday/Friday 3 weeks on/1 week off for 12 weeks (**cohort 2, n=2)**
  - 20 mg/d PO for Monday/Wednesday/Friday for 12 weeks (**cohort 3, enrolling**)

- **Cohort 1:** HbF: 7.9-> 8.2 % and in F-cells: 7.6-> 19.7%
- **Cohort 2:** HbF: 14.9 % -> 19.6% and F-cells 12.9 -> 20.6% (day 85).

Kutlar A Blood 146: 613, 2025

Pociredir binding to embryonic ectoderm development (EED) subunit, reducing BCL11 and MYB increases HbF expression



Pociredir is a potent EED binder

- Highly selective
- Clean off-target profile
- Robust target engagement observed at doses as low as 2 mg

ED, embryonic ectoderm; HbF, fetal hemoglobin; mRNA, messenger RNA; PRC2, polycomb repressive complex
Stuart B, et.al., Hemasphere 2022; Sheinel A et al. Blood 146: 1157, 2025

Modified from M. Steimberg

PIONEER: A Phase 1B Study in Patients With SCD

Study Design (Open Label, Dose Escalation, ≈10 Patients per Cohort)

4-Week Screening Period

12-Week Treatment Period (QD Capsule)

- Cohort 1 6 mg (n=10)
- Cohort 2 2 mg (n=2)
- Cohort 3a 12 mg (n=4)
- Cohort 3b 12 mg (n=16)

Completed (previously presented)

- Cohort 4 20 mg (n=13) — Initial 20 mg Cohort 4 data presented at ASH — In Progress

4-Week Follow-Up Period

Select Inclusion Criteria

- SCD Patients 18-65 years
- Discontinued HU for ≥60 days
- Severe SCD as defined by ≥4 VOCs over 12 months or ≥2 VOCs over 6 months

Key Study Endpoints

Primary
- Safety and tolerability assessments
- PK parameters

Secondary
- HbF induction
- Hemolysis
- Anemia

Exploratory
- Globin gene expression
- % F-cells
- Incidence of VOCs

Additional criteria apply. For more information, please see https://www.clinicaltrials.gov/study/NCT05169580.
HbF, fetal hemoglobin; HU, hydroxyurea; QD, once daily; SCD, sickle cell disease; VOC, vaso-occlusive crisis; PK, Pharmacokinetic; F-Cells, Cells expressing Fetal Hemoglobin
Modified from Alan S, et al. *J Sick Cell Dis.* 2025;2(Suppl 1); Sheinel A et al. Blood 146: 1157, 2025

Modified from M. Steimberg

Pociredir increases HbF expression and F-cells in adult patients with SCD

- **20 mg Pociredir** increased %HbF from 7.1% to 16.9% at Week 6 (n=12)
- 7 of 12 patients (58%) achieved a ≥20% absolute level of %HbF at their latest study visit (*ad interim evaluation*)
- **All patients in the 20 mg cohort achieved a ≥6.5% absolute HbF increase from baseline** with pancellular distribution
- Patients with complete 12-week data (n=6) in the 20 mg cohort achieved >3.75-fold induction of HbF, demonstrating a clear dose-response

Sheinel A et al. Blood 146: 1157, 2025

In adult patients with SCD, Pociredir significantly reduces markers of hemolysis and improves anemia with a reduction in VOCs

- 27 to 38% reduction in LDH (respectively in 12 and 20 mg cohorts)
- 37% reduction indirect bilirubin (in both 12 and 20 mg cohorts)
- 31-37% reduction in reticulocyte count
- Increased Hb (12 mg: mean Hb 7.8->8.7 g/dl at 84 weeks; 20 mg: 7.3-> 8.1 g/dL at 42 weeks)

50% of SCD pts (8/16) did not experience VOCs

Sheinel A et al. Blood 146: 1157, 2025

In adult patients with SCD, Pociredir AE:

- Back pain/ extremity pain (31%)
- Fatigue (25%)
- Arthralgia (19%)
- Headache, nausea, diarrhea in 3 pts

- 3 patients reported treatment-related AEs
  - All treatment-related AEs resolved during treatment period (
  - Grade 3 Reticulocytopenia alongside broader CBC reductions in the context of a viral infection (presumed Parvo B19) and amoxicillin treatment. 14-day pociredir treatment interruption. Continued normalization of CBCs following re- exposure to pociredir (n=1)
  - Insomnia (n=1), iron overload (n=1)

- No dose limiting toxicities or dose discontinuations due to treatment-related AE

Sheinel A et al. Blood 146: 1157, 2025

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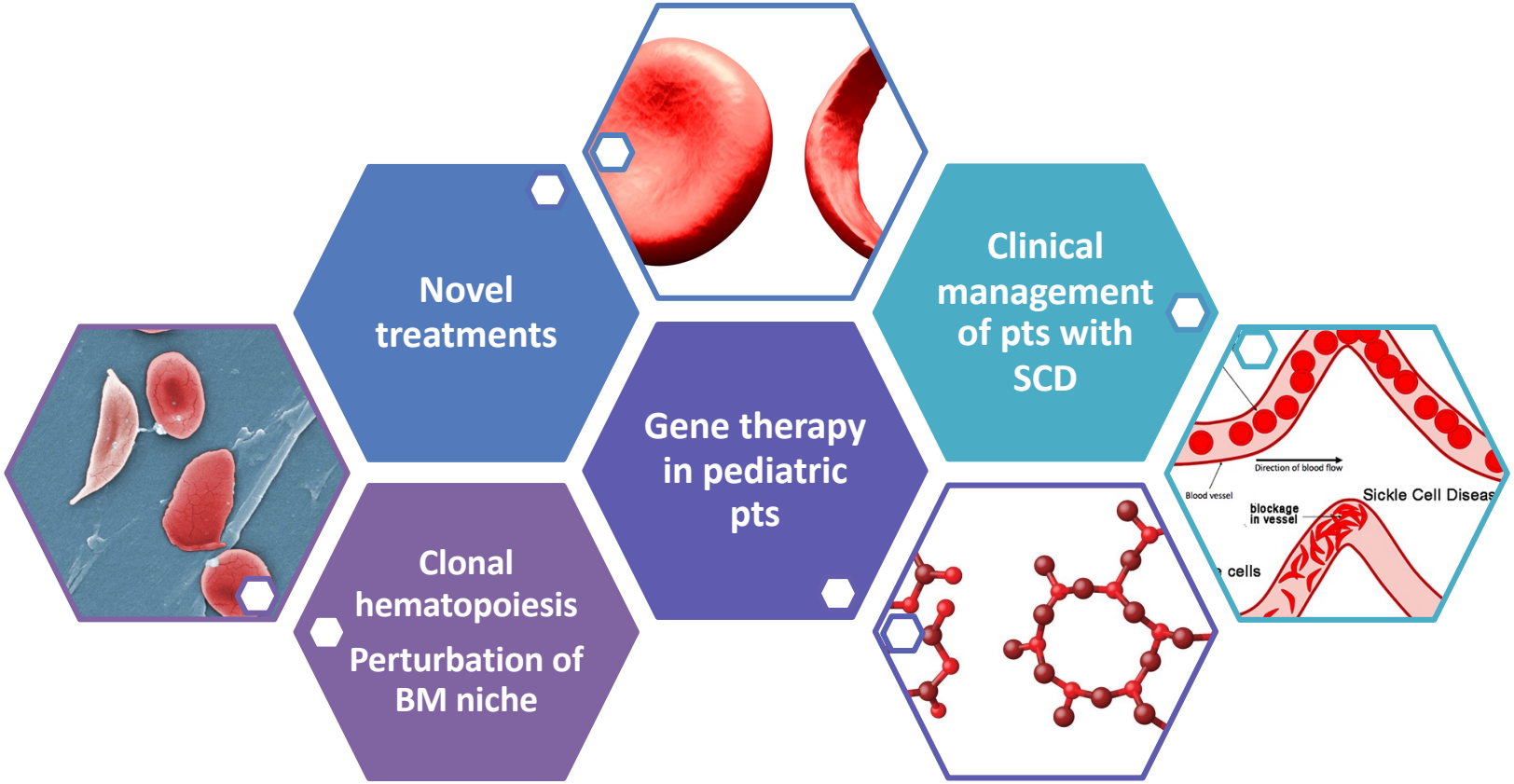


Ad interim results CLIMB THAL-141 (TDT) and CLIMB SCD-151 (SCD) are ongoing 2-y, Phase 3 trials of exa-cel in participants (pts) aged 2-11 y

- **Inclusion criteria:**
  - TDT with history of ≥100 mL/kg/y or ≥10 U/y of packed red blood cell (RBC) transfusions for 2 y before screening
  - SCD a history of ≥2 severe VOCs per y for 2 y before screening

- **Primary endpoints:**
  - **In CLIMB THAL-141,** the primary endpoint is transfusion independence: proportion of pts maintaining a weighted average Hb ≥9 g/dL without RBC transfusion for ≥12 consecutive months (mo; TI12).
  - **In CLIMB SCD-151**, the primary endpoint is proportion of pts free of severe VOCs for ≥12 consecutive mo (VF12); key secondary endpoint is proportion of pts free from inpatient treatment of severe VOCs for ≥12 consecutive mo (HF12).

Frangoul H et al Blood 146: 379, 2025

- **13 TDT children <12 y** (mean age 7.4 [range 5, 11] y; 61.5% male)-> β0/β0 or β0/β0-like genotypes-> median follow-up 12.6 mo

- As of the datacut, **9/13 pts were transfusion-free** and **5/5 pts evaluable for the primary efficacy endpoint achieved TI12, with the longest transfusion-free duration of 19.1 mo**.

- Mean total Hb increased to ≥11.8 g/dL by Mo 6, which exceeds the age adjusted LLN, and was stable thereafter. Mean HbF increased to ≥11.0 g/dL by Mo 6 and was stable thereafter.

One 6-years old TDT pt developed severe veno-occlusive disease (VOD; related to busulfan multi-organ failure that was fatal.

Frangoul H et al Blood 146: 379, 2025

- **10 SCD children <12 y** (mean age 8.2 [range 5, 11] y; 50.0% male)-> β^S/β^S genotype -> median follow-up 8.5 mo

- No pts had VOCs after exa-cel infusion, with longest duration VOC-free of 20.7 mo.

- 2/2 evaluable pts achieved VF12 and HF12. Increases in HbF were similar to adults and adolescents. Mean HbF% >40% was achieved by Mo 6 and was durable with a pancellular distribution and normal total Hb

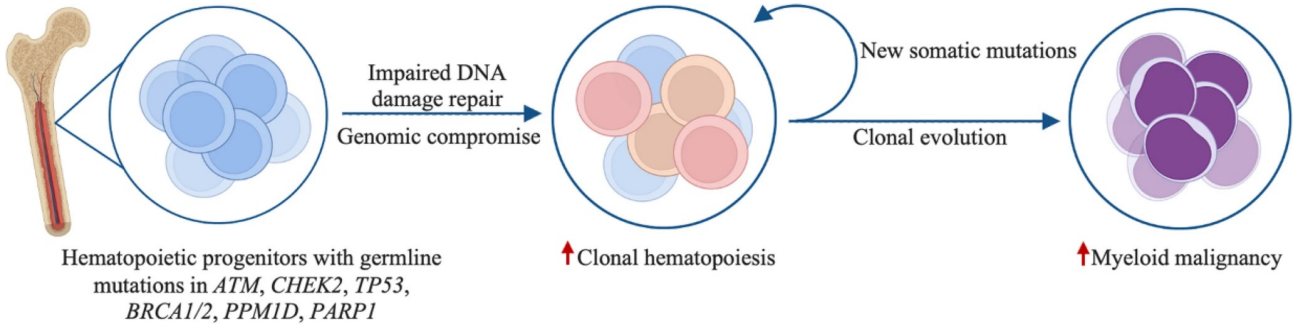
Frangoul H et al Blood 146: 379, 2025

SCD patients display increased risk of myeloid malignancies

- Increased incidence of acute myeloid malignancies has been described in two large cohorts of patients with SCD compared to matched healthy population.
- The prevalence of clonal hematopoiesis has been reported to be increased in patients with SCD older than 40 years of age.
- Two cases of acute myeloid leukemia (AML), and one of myelodysplastic syndrome progressing to AML, in adult patients with SCD treated with lentivirus-based gene therapy, even if a possible relation with the procedure has been excluded.

Seminog OO, *J R Soc Med*. 109:303, 2016 Brunson A, et al. *Blood*. 130:1597, 2017; Hsieh MM, et al. *Blood Adv*. 4:2058, 2020; Sunita G, John T, et al. *New England Journal of Medicine*. 386:138, 2022; Kanter J, et al. *Am J Hematol*. 98:11, 2023; Ribeil JA. *Am J Hematol*.97:4, 2022.

Somatic mutations and patients with SCD from pediatric to young adult population



- DNA analyses by duplex sequencing: 17 cohorts involving 7283 patients from 4 countries
- Panel analyzed:
  - **DDR-clonal hematopoiesis (CH):** TP53, PPM1D, CHEK2, ATM
  - **DT-CH:** DNMT3A, TET2

Fedorov K et al Curr Hematol Malign Rep 20, 2025; Weeks L et al Blood 146: 8, 2025

SCD Is Associated With Predisposition To High Risk of Clonal Hematopoiesis

- **Increased prevalence PPM1D (DDR-CH) was** 29; 20-29; 40-49 years) when compared to h
- **Increased prevalence of DT-CH in** youngest S to healthy controls
- In cohort from BabyHUG trial (0.6-1.4 years) obtained 3-11 years of age:
  - Baseline: DDR-CH was present in 4.7 % children
  - Follow-up: appearance of DDR-CH in 3.9% of ch

- DDR-CH/DT-CH was similar in AC/AS and AA
- In β thal pts (n=181) the prevalence of CH was similar to healthy controls

Weeks L et al Blood 146: 8, 2025

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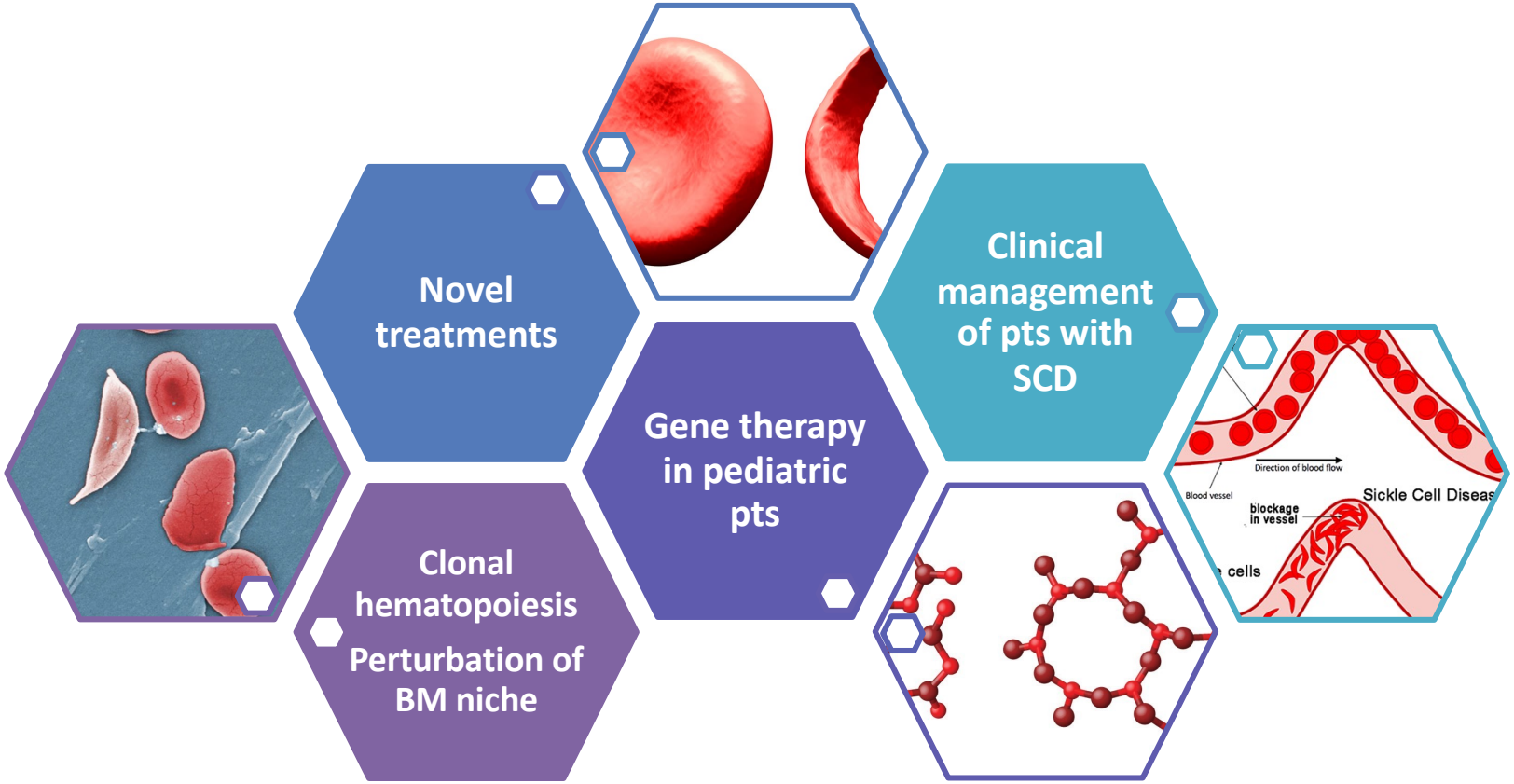


HU and clinical management of SC patients

- SC is the second most prevalent genotyp
- Treatment of SC patients is still largely ba
  experience and limited data are available
  the risk of hyperviscosity from the HU inc
- Single center retrospective study in SC a
  from 2010 to 2025 with 12 months follov
  70), baseline Hb 11.8 g/dL-> median dose

- Reduction of VOCs in 56% of SC pts (greater reduction in pts aged 18-30 yrs and those with α-thal)
- No signs of hyperviscosity even in 10.9% of SC pts with Hb > 12 g/dL

Girard A et al Blood 146: 11660, 2025

HU and pregnancy in patients with SCD

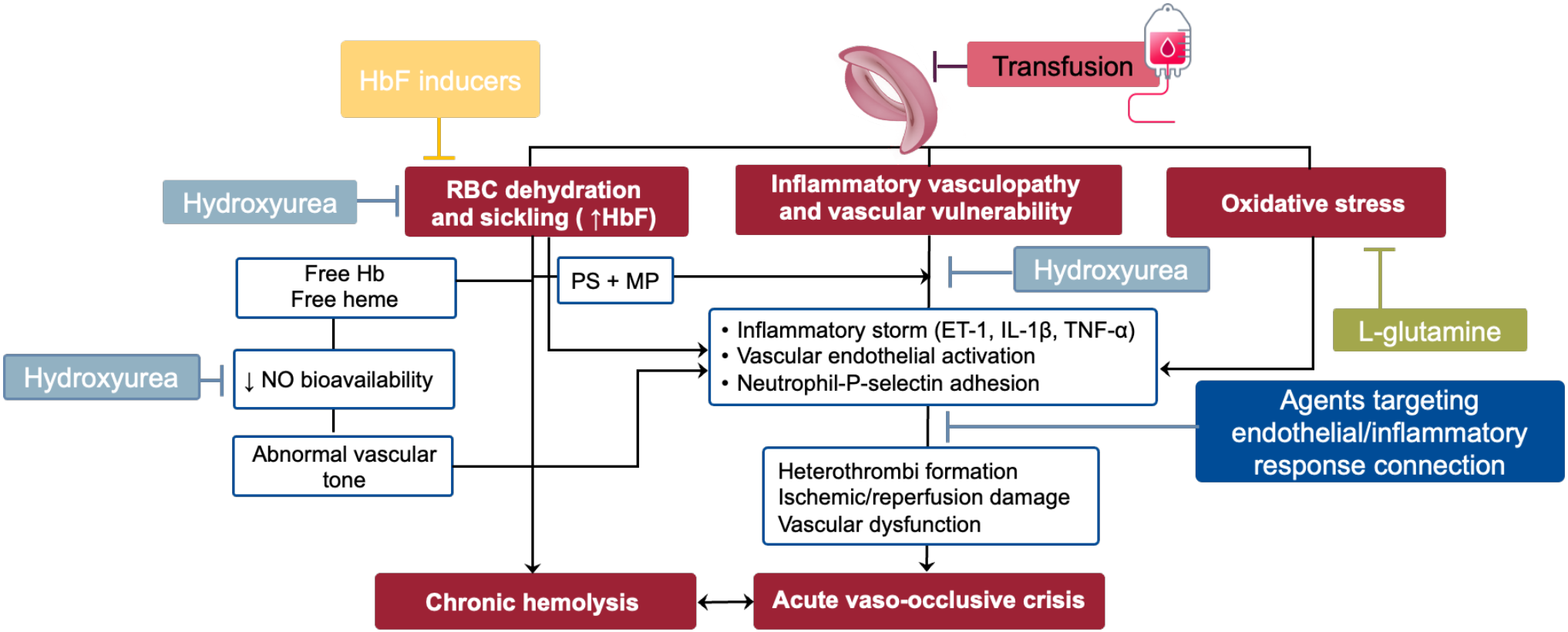
- ESCORT-HU/extension: European SCD cohort –H Germany, Italy) 2009-2019; 2020-2025
- 246 pregnancy in 202 SCD women ->
  - age: 31.3±5.6 years, me
  - Median HU exposure: 6 years (1.6-6.6 years)
  - Mean dose 16.5 ±7.5 mg/Kg/d
- HU was stopped few months before pregnancy
- HU was continued during the first trimester:
  - 18 undergoing voluntary abortion
  - 176: live births (76%), premature birth (27%), misca

- Fertility of women on HU is preserved.
- Most of the pregnancy happen during HU treatment indicating unplanned pregnancy.
- **No malformation of newborns in maintaining HU during the first trimester.**

Habibi A et al Blood 146: 2, 2025

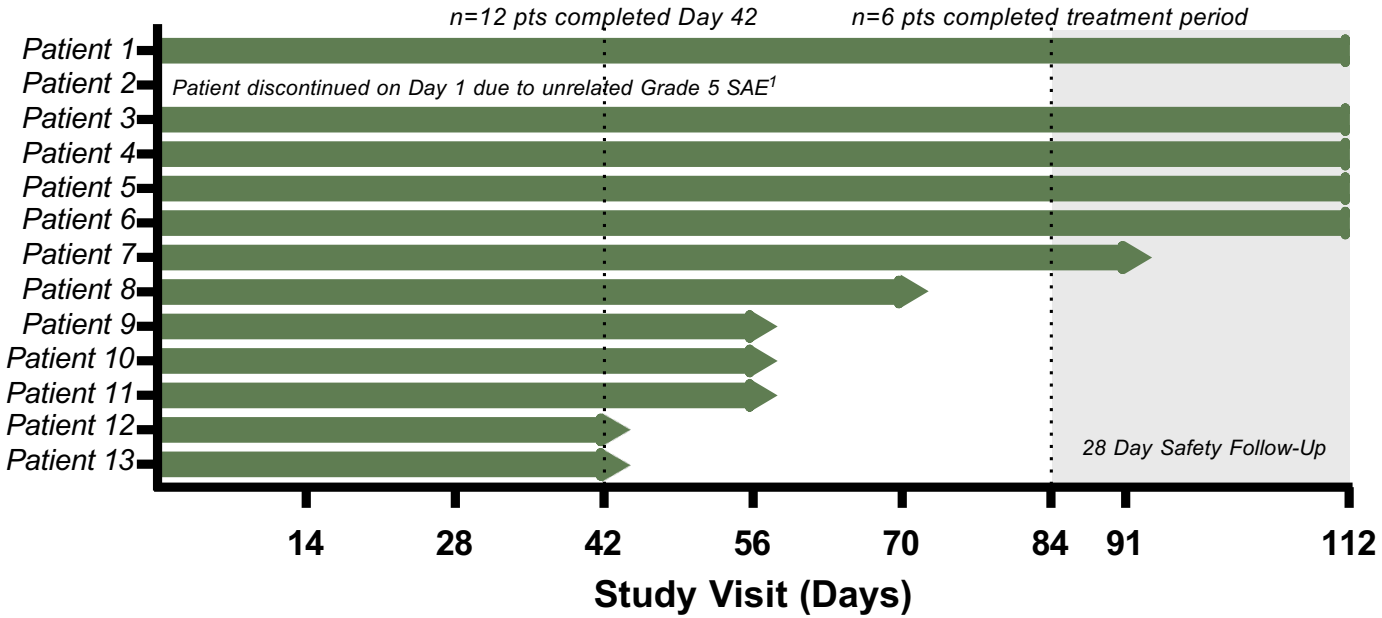
Conclusions

- **Novel treatments:**
  - Phase-1 studies on new therapeutic agents modulating HbF synthesis act on HDAC isoforms or decreasing the expression of repressors of HbF synthesis as BCL11a
  - Update on 5-12 years old pts with hemoglobinopaties undergoing GE, with results similar to young adult pts.
- **Evidence of perturbation of BM niche:**
  - Increase prevalence of clonal hematopoiesis in SCD patients across age when compared to healthy subjects
- **Clinical management of pts with SCD:**
  - Evidence of safety of HU in SC pts
  - No malformation of newborns in maintaining HU during the first trimester



De Franceschi L, et al. *Sem Thrombosis*. 2011;37:266; De Franceschi L. *Haematologica.* 2015;100(S3):195-7; Matte A et al. *Mediterr J Hematol Infect Dis.* 2019;11:e2019002; Matte A, et al. *Exp Opinion Invest Drugs*. 2020; 29: 23-31; Italia K, et al. *PLoS One*. 2013;8(12):e82928; Pinto VM et al Blood 2024.

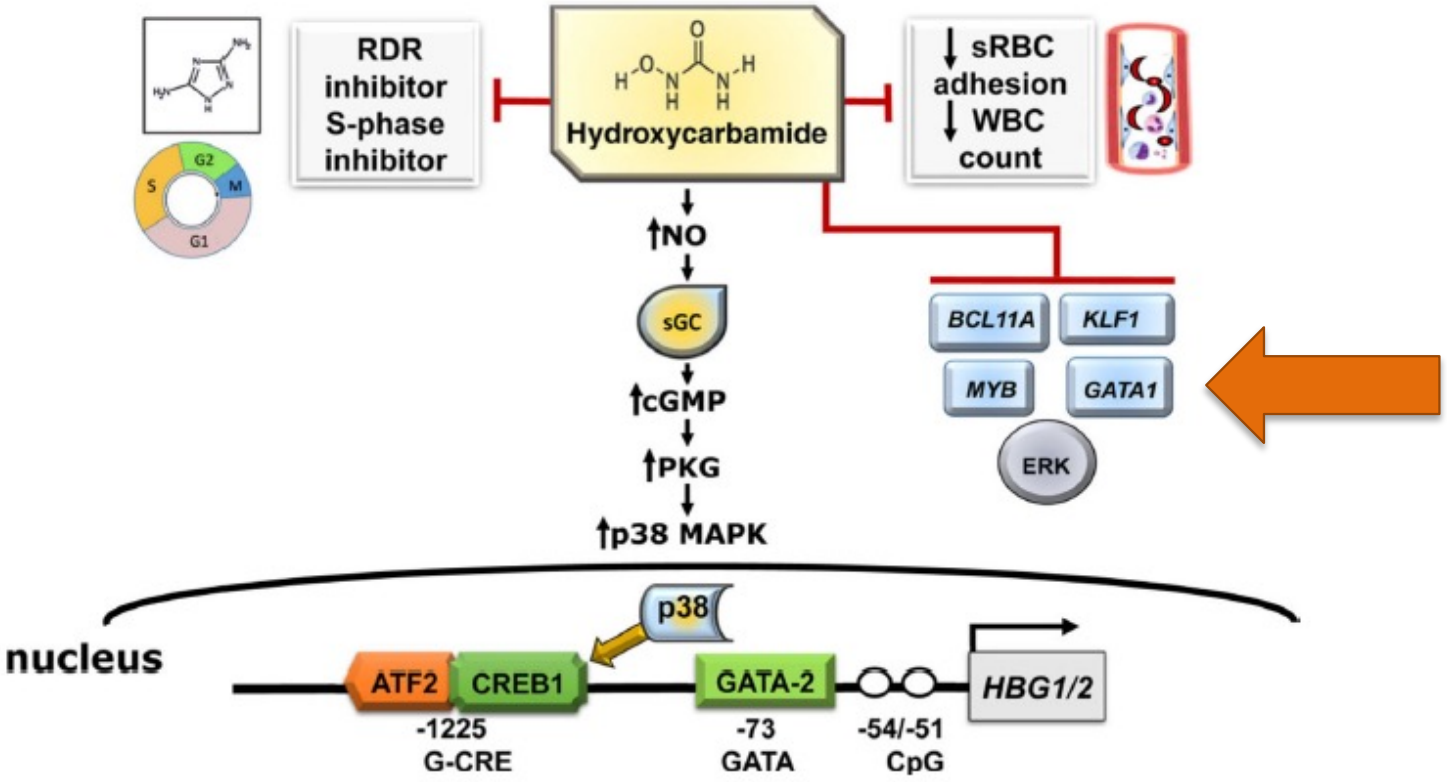
20 mg Cohort Patient Disposition (Data Cut: Nov 11, 2025)



- 20 mg Pharmacodynamic (PD) Analysis Set includes n=12 patients. 6 of 12 patients (50%) have reached 12 weeks and 12 of 12 patients (100%) had reached at least 6 weeks as of data cut. [25]
- Safety Analysis Set to be presented includes all 12 mg (n=16) and 20 mg (n=13) data as of data cut
- Continued high adherence (97%) to treatment schedule in the 20 mg cohort[2]

Disposition and all subsequent data as of Nov 11, 2025, data cut

1. Grade 5 SAE determined by the investigator unrelated to treatment following complications from VOC reported on Day 1 of study. Patient excluded from the PD Analysis Set
2. Adherence measured via AiCure®, an artificial intelligence data collection tool providing real-time feedback and data collection to measure and improve study drug adherence. Dosing interruptions on study not included in AiCure adherence analysis



Pace SB et al. BJH 194: 240, 2021