44° CONVEGNO NAZIONALE di Studi di Medicina Trasfusionale
Rimini | Palacongressi, 3-5 maggio 2022
SIMTI

Nuovi approcci terapeutici nelle Emoglobinopatie

Gian Luca Forni

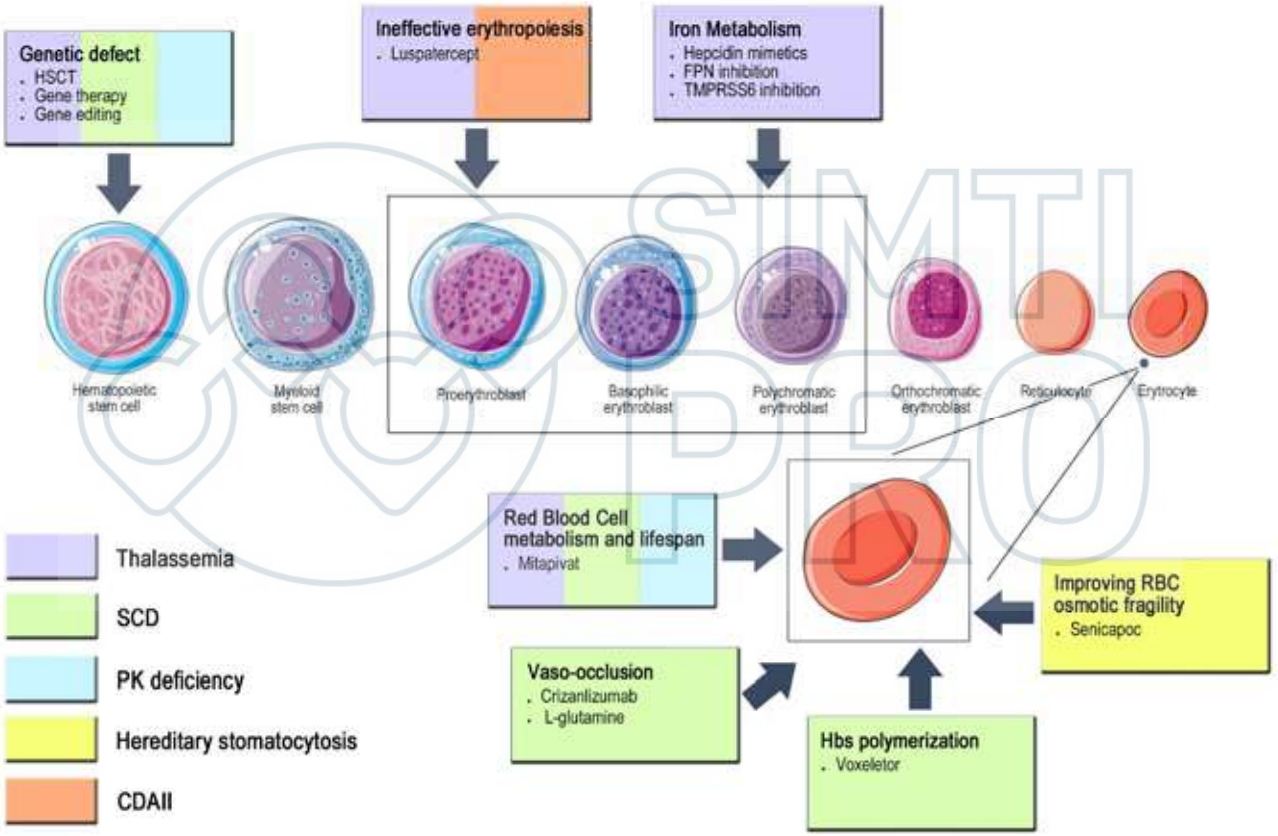
Centro della Microcitemia ed Anemie Congenite

Ospedale Galliera-Genova

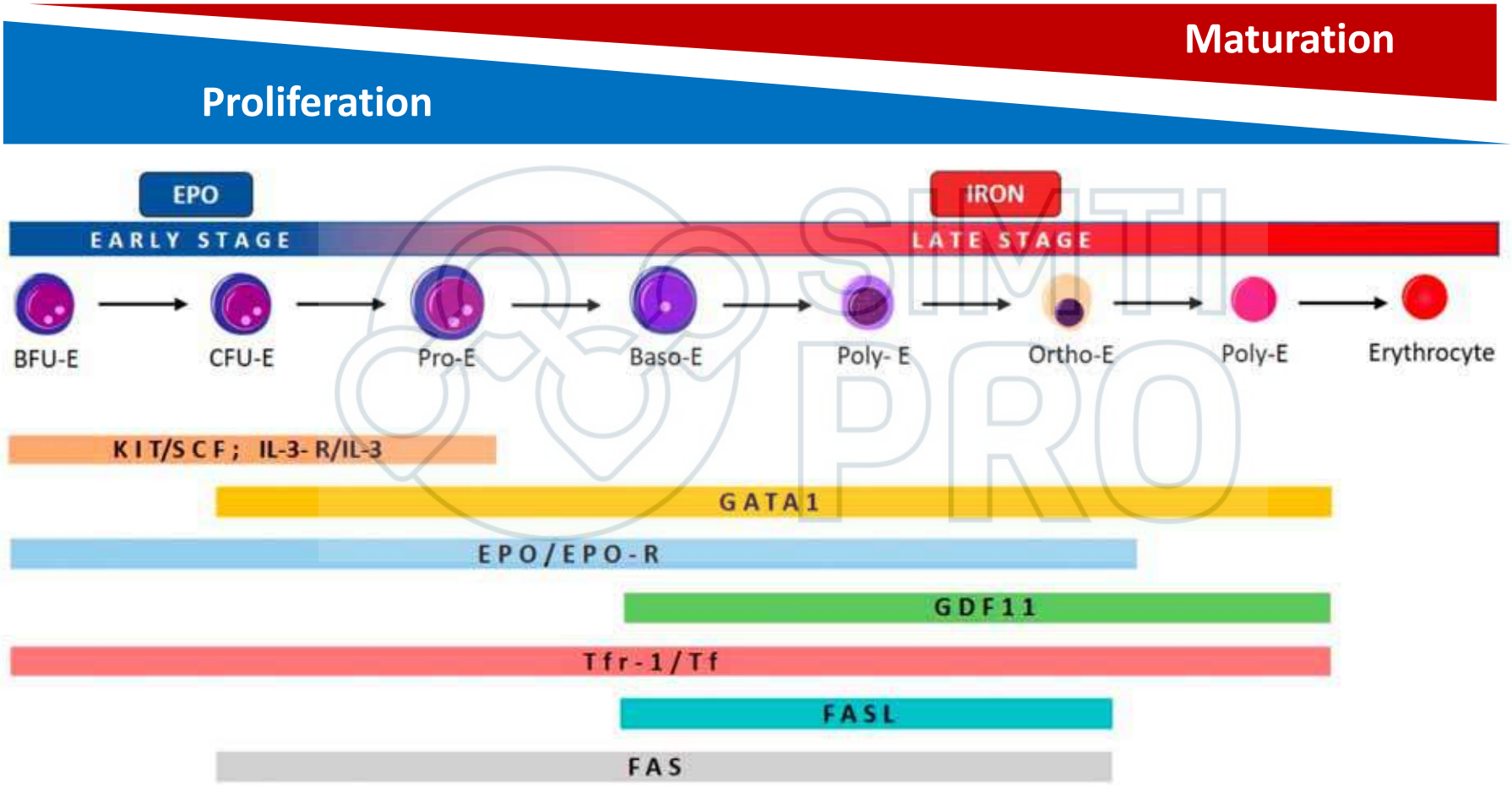
Il sottoscritto, in qualità di Relatore
dichiara che *negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con i soggetti portatori di interessi commerciali in campo sanitario:*

-Novartis
-Celgene BMS
-Vertex
- Agios

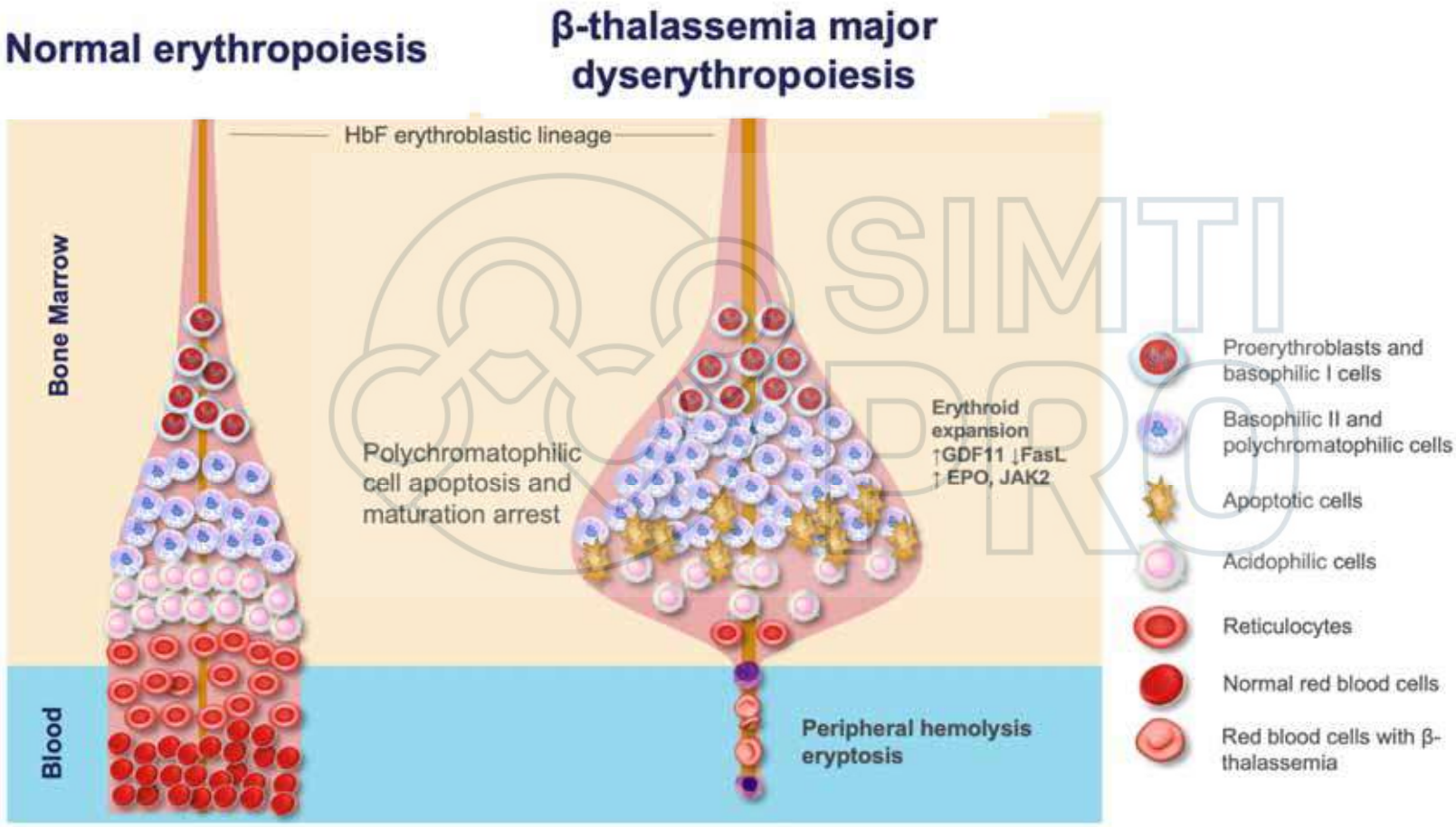
Emoglobinopatie: nuovi approcci terapeutici



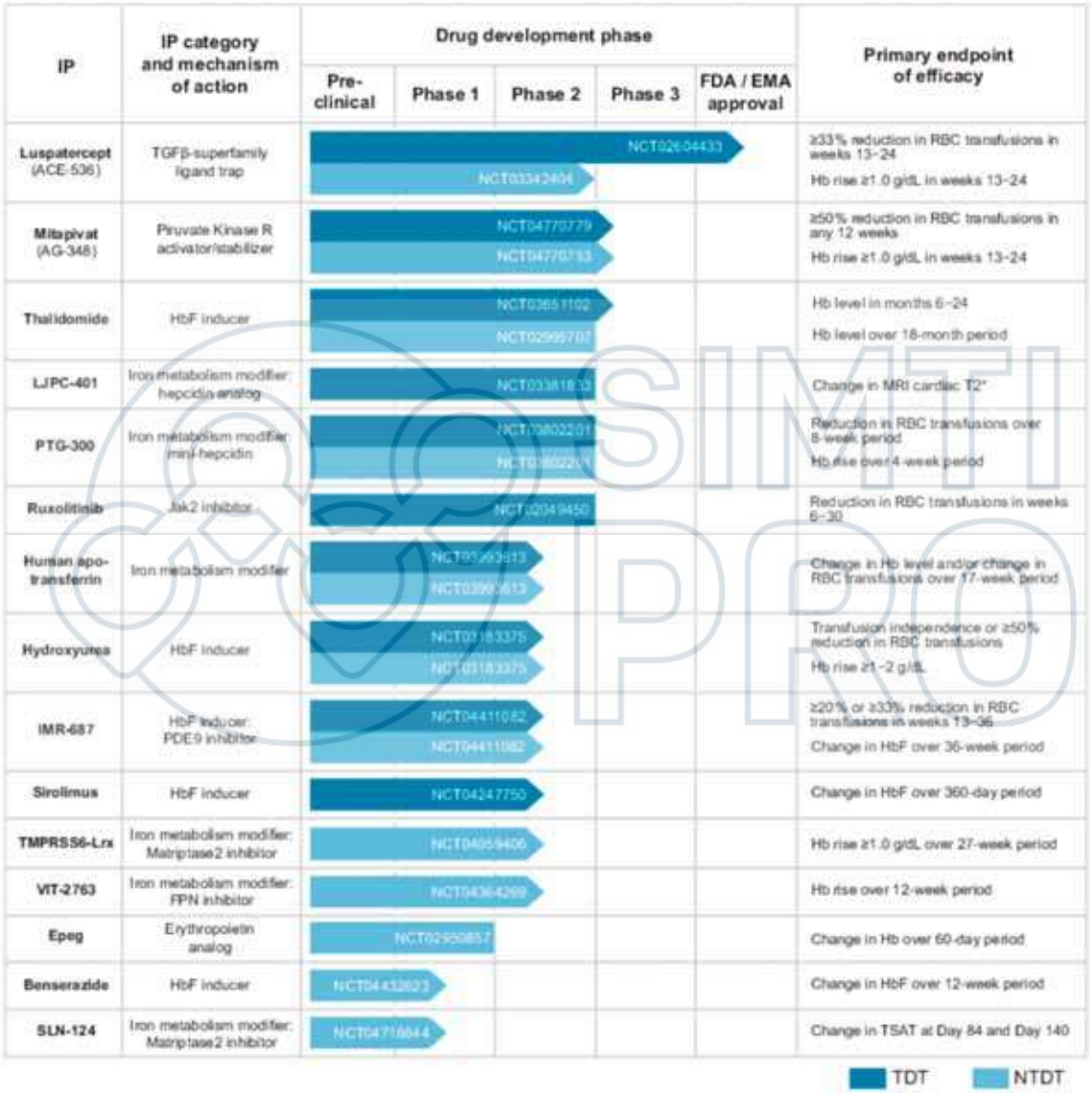
Cappellini MD, submitted



Adapted from Parisi S, *IJMS*, 2021



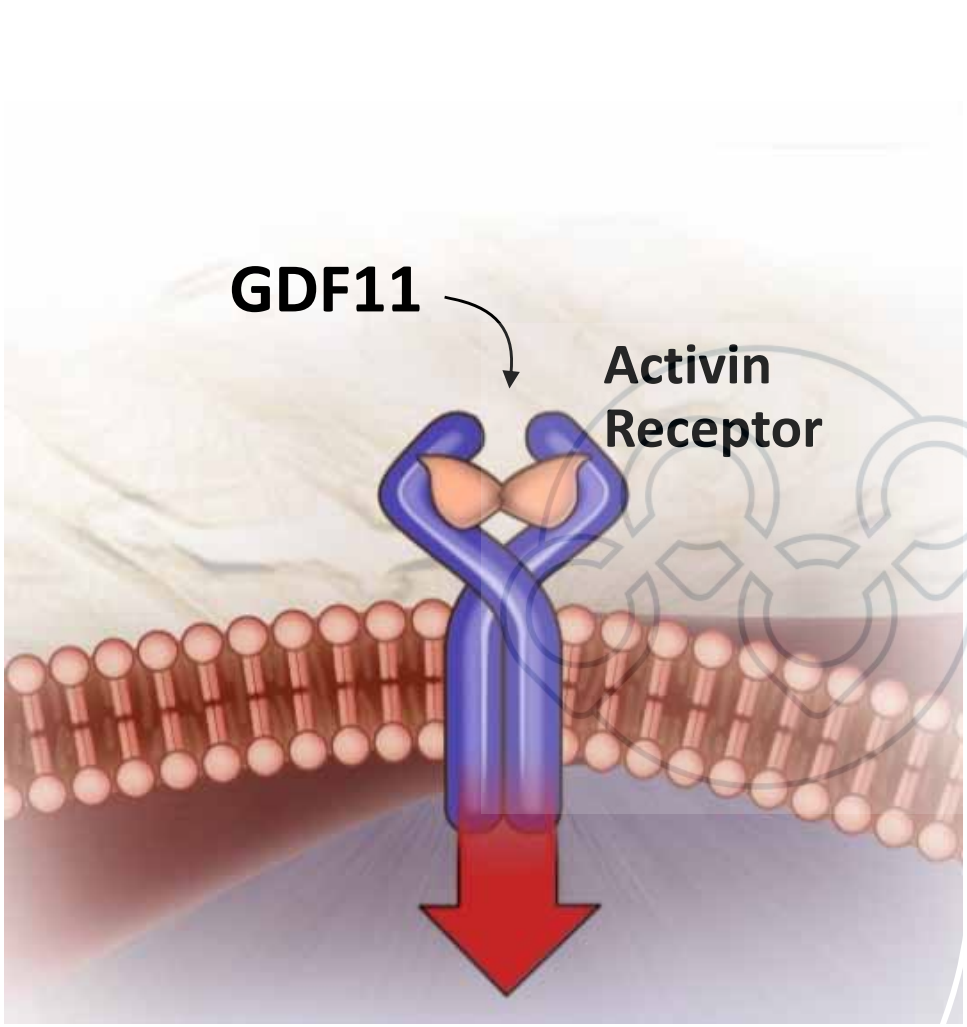
Adapted from Arlet J.B. et al, IJMS, 2021



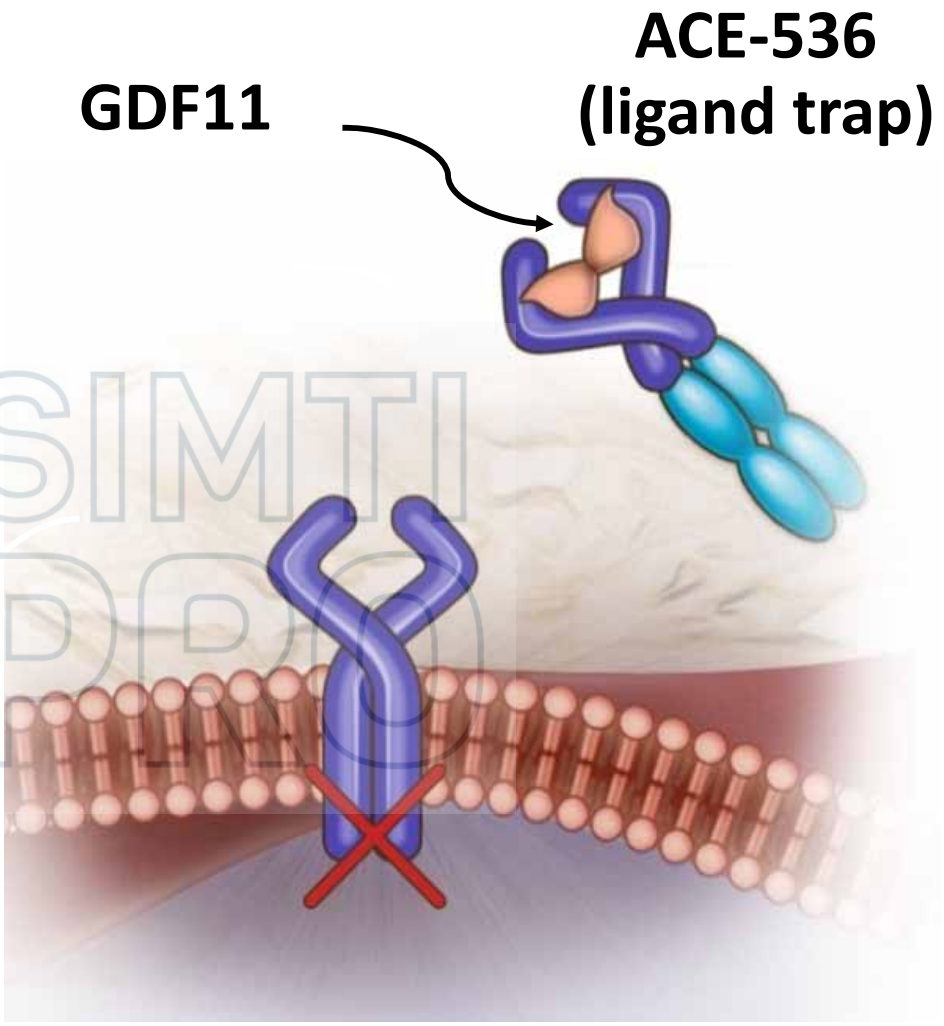
Longo F, *IJMS*, 2021

Luspatercept approval

Luspatercept has been approved by the US Food and Drug Administration (FDA) in 2019 and by the European Medicines Agency (EMA) in 2020 and by the AIFA in 2021 to treat anemia in adult patients with beta-thalassemia who require regular red blood cell transfusions

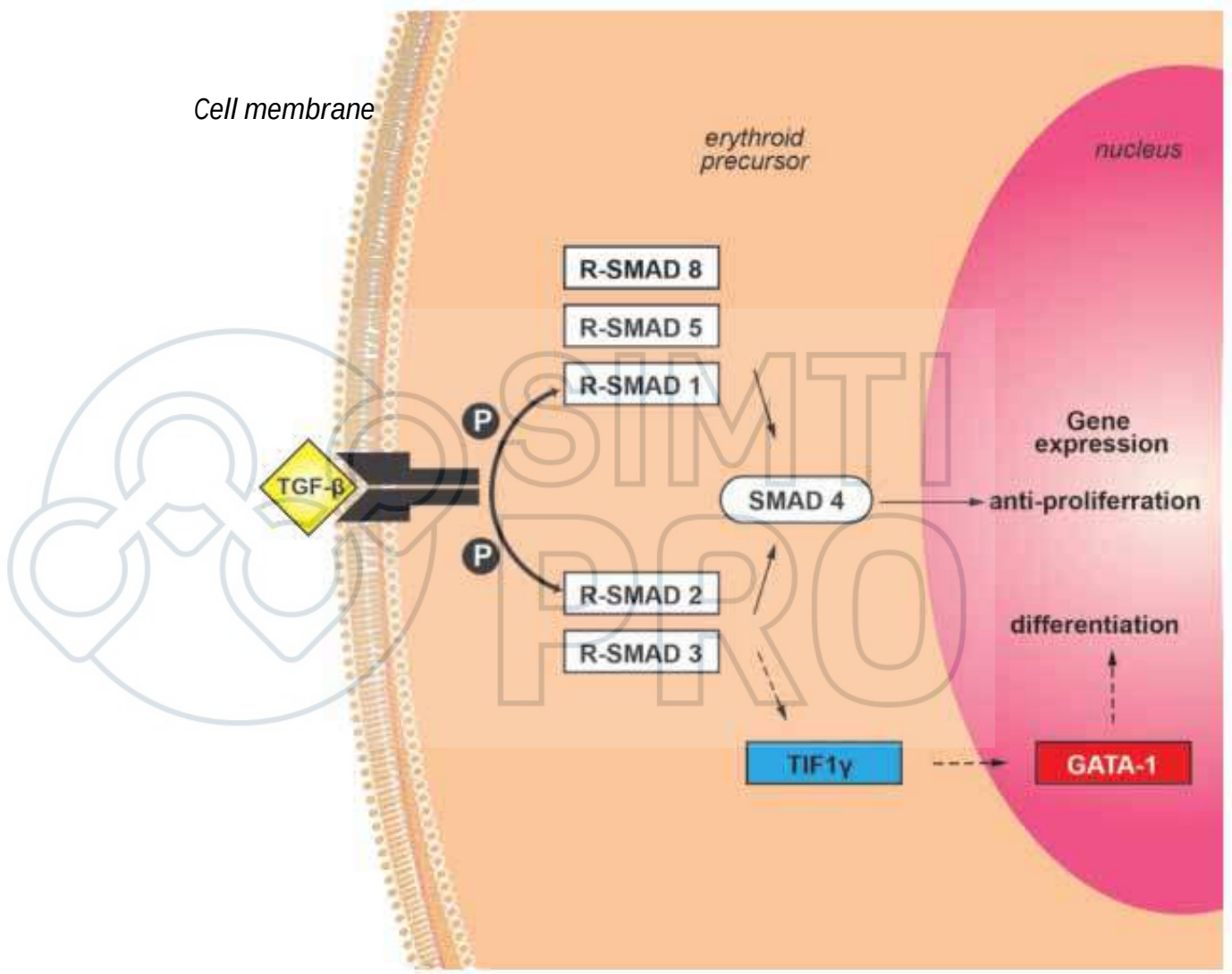


Smad 2,3 signaling
inhibits RBC Maturation

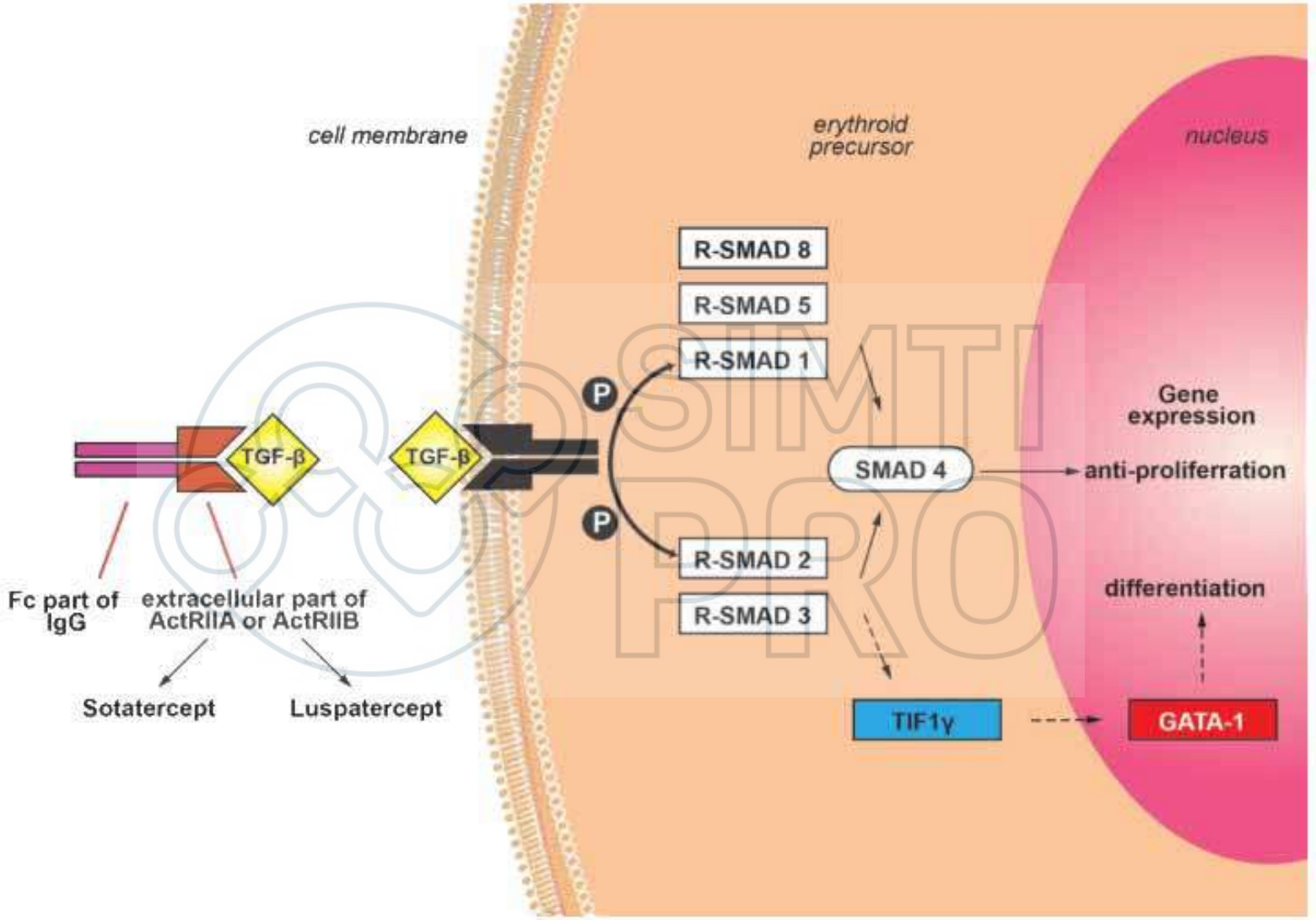


Reduced Smad 2,3 signaling -
promotes RBC Maturation

NORMAL

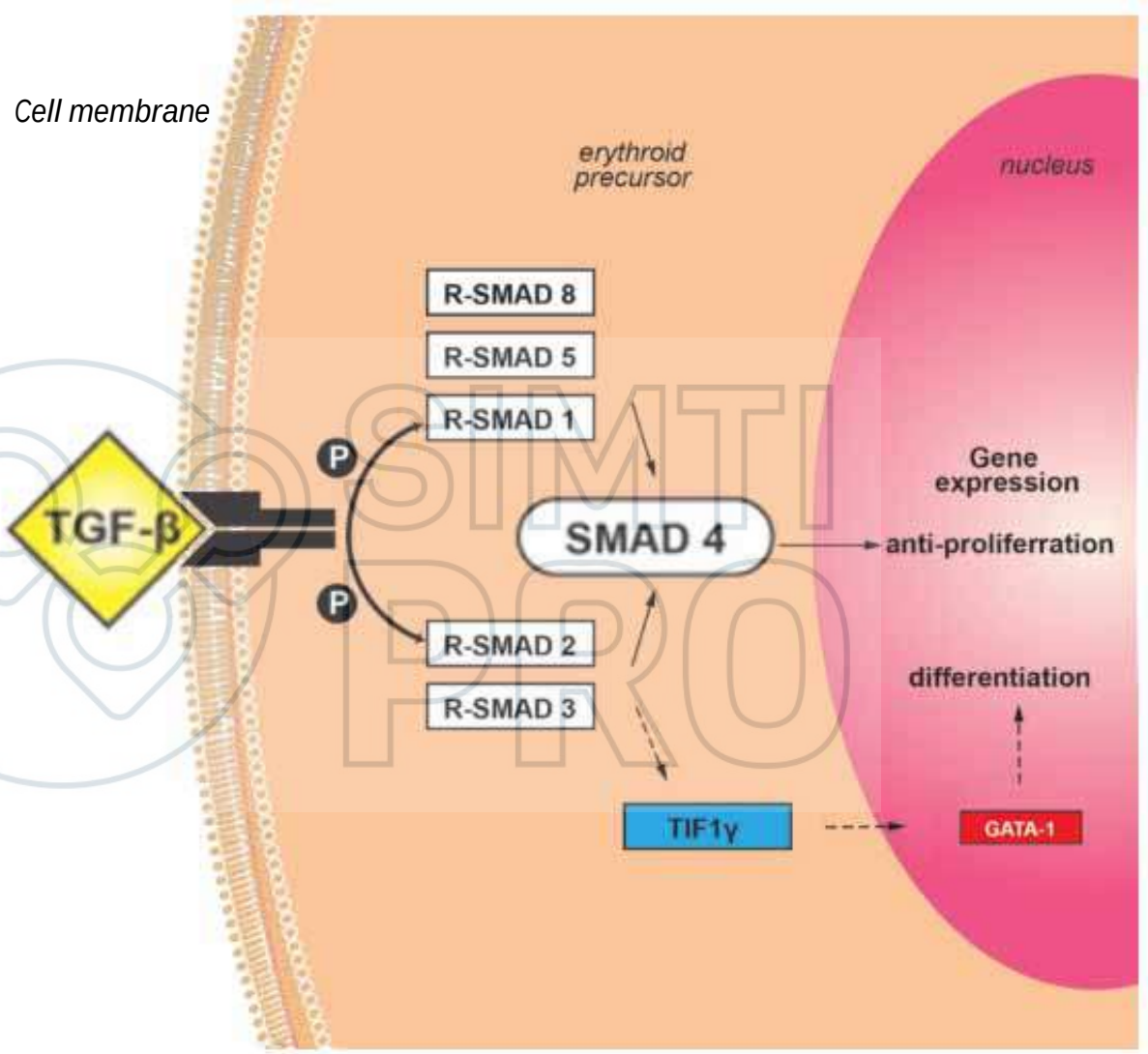


Adapted from Makis A, *Biology*, 2021



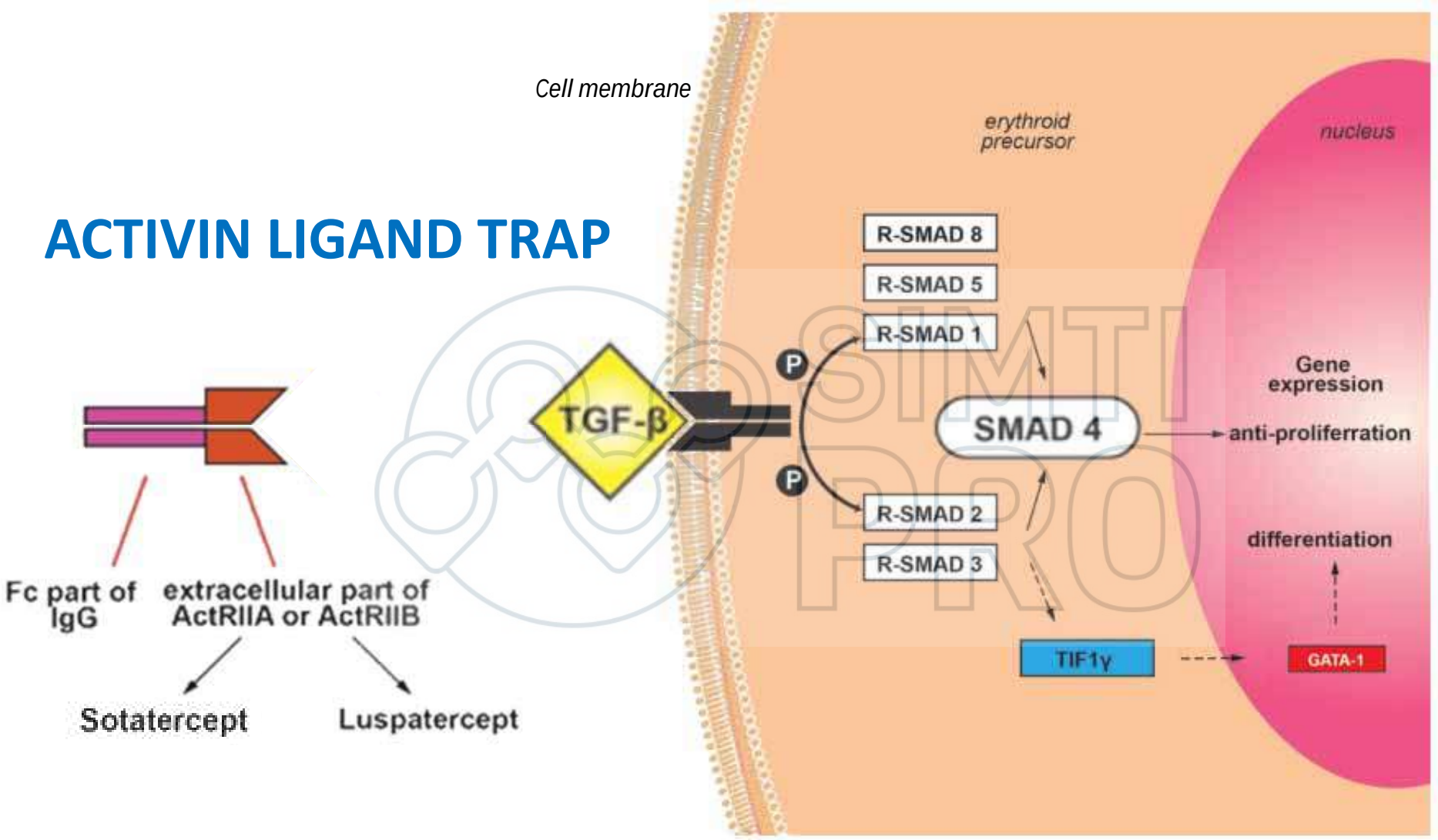
Adapted from Makis A, *Biology*, 2021

THALASSEMIA



Adapted from Makis A, *Biology*, 2021

ACTIVIN LIGAND TRAP



Adapted from Makis A, *Biology*, 2021

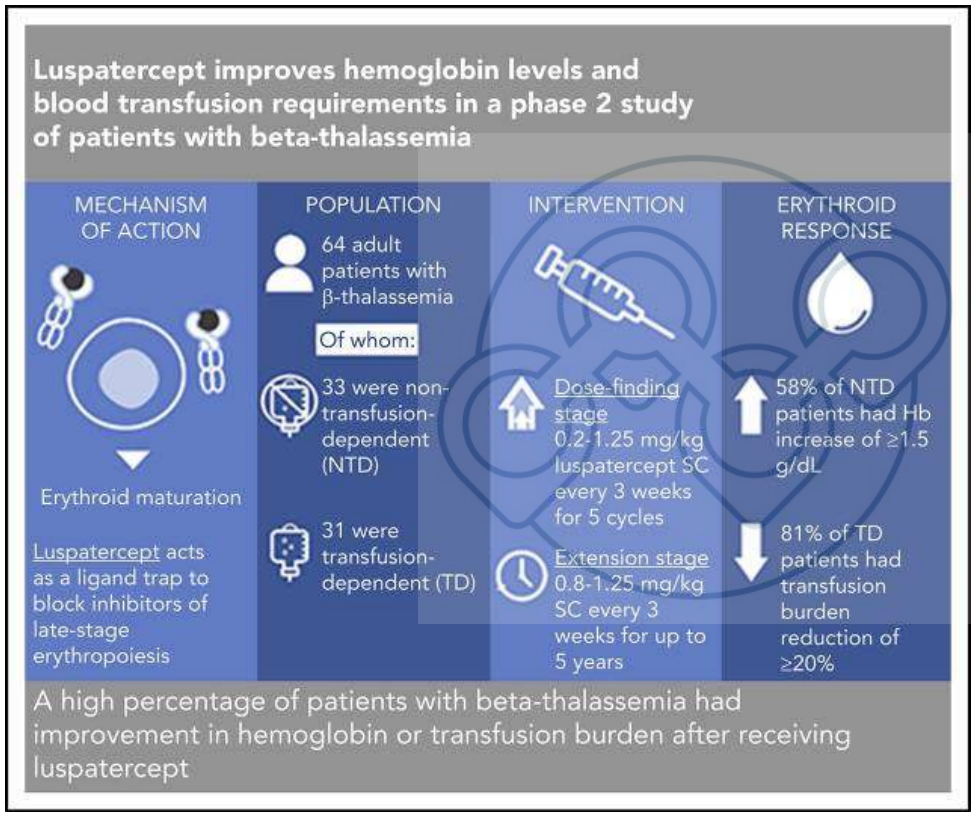
Luspatercept and Sotatercept (erythroid maturation agents) trials

Agent	Clinical Trials*	Design	n‡, population, age	Key efficacy measures
Erythroid maturation agents				
Luspatercept (ACE-536)	• NCT01749540 • Completed†	• Phase 2 • Open-label	• n = 64 • TDT, NTDT with Hb <10 g/dL • ≥18 yr	• TDT: Transfusion reduction (≥20%)§ • NTDT: Hb increase ≥1.5 g/dL§, Hb • Biomarkers of erythropoiesis, hemolysis, iron metabolism, bone metabolism
	• NCT02268409 • Completed	• Phase 2 extension	• n = 51 • TDT, NTDT included in phase 2	• TDT: Transfusion reduction (any, ≥20%, ≥50%), Hb • NTDT: Hb increase ≥1.5 g/dL, Hb • Reticulocytes, EPO, nRBC, sTfR, SF, TIBC, TSAT, NTBI • HR-QoL
	• BELIEVE • NCT02604433 • Active, not recruiting†	• Phase 3 • Randomized, placebo-controlled, double-blind	• n = 336 • TDT • ≥18 yr	• Transfusion reduction (≥33%§, ≥50%) • Transfusion requirement • Transfusion independence • SF, LIC, MIC, ICT use • BMD • HR-QoL, healthcare resource utilization
	• NCT04143724 • Not yet recruiting	• Phase 2 • Open-label	• n = 46 • TDT • 6 months-18 yr	• Transfusion reduction • Hb
	• BEYOND • NCT03342404 • Active, not recruiting	• Phase 2 • Randomized, placebo-controlled, double-blind	• n = 145 • NTDT with Hb ≤10 g/dL • ≥18 yr	• Hb increase (any, ≥1 g/dL§, ≥1.5 g/dL) • Transfusion requirement • PRO, HR-QoL, 6MWT • SF, LIC, ICT use
Sotatercept (ACE-011)	• NCT01571635 • Active, not recruiting†	• Phase 2 • Open-label	• n = 46 •TDT, NTDT • ≥18 yr	• Transfusion reduction (any, ≥20%) • Hb

*Status per clinicaltrials.gov on 09 April 2021; †Available interim or final results; ‡Actual or estimated, per clinicaltrials.gov on 09 April 2021; §Primary endpoint.

Musallam KM et al. Am J Hematol 2021; Submitted; Piga A et al. Blood 2019;133:1279-89; Cappellini MD et al. N Engl J Med 2020;382:1219-1231; Cappellini MD et al. Haematologica 2019;104:477-484.

Luspatercept: key findings from the phase 2 trial



Piga A et al. Blood 2019;133:1279-1289.

blood

Plenary Paper

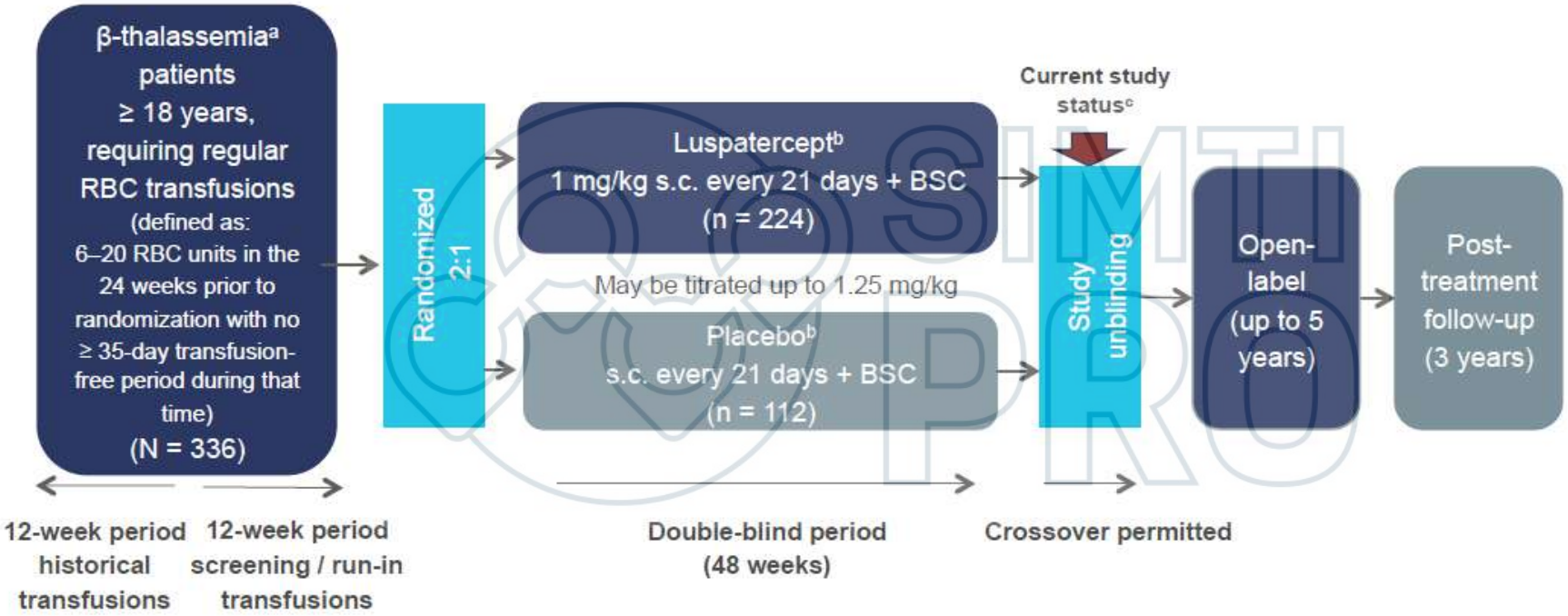
CLINICAL TRIALS AND OBSERVATIONS

Luspatercept improves hemoglobin levels and blood transfusion requirements in a study of patients with β-thalassemia

Antonio Piga,[1] Silverio Perrotta,[2] Maria Rita Gamberini,[3] Ersi Voskaridou,[4] Angela Melpignano,[5] Aldo Filosa,[6] Vincenzo Caruso,[7] Antonello Pietrangelo,[8] Filomena Longo,[1] Immacolata Tartaglione,[2] Caterina Borgna-Pignatti,[9] Xiaosha Zhang,[10] Abderrahmane Laadem,[11] Matthew L. Sherman,[10] and Kenneth M. Attie[10]

[1]Department of Clinical and Biological Sciences, Turin University, Turin, Italy; [2]Dipartimento della Donna, del Bambino e della Chirurgia Generale e Specialistica, Università degli Studi della Campania "Luigi Vanvitelli," Naples, Italy; [3]Thalassemia Unit, Arcispedale S. Anna, Ferrara, Italy; [4]Laiko General Hospital, Athens, Greece; [5]Ospedale "A. Perrino," Brindisi, Italy; [6]Rare Red Blood Cell Disease Unit, Cardarelli Hospital, Naples, Italy; [7]Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione Garibaldi, Catania, Italy; [8]Centro Emocromatosi e Malattie Eredometaboliche del Fegato, Medicina 2, Modena, Italy; [9]Section of Pediatrics, Department of Medical Sciences, University of Ferrara, Ferrara, Italy; [10]Acceleron Pharma, Cambridge, MA; and [11]Celgene Corporation, Summit, NJ

BELIEVE: a randomized, double-blind, placebo-controlled, phase 3 study of luspatercept in adults with TDT



[a] β-thalassemia or hemoglobin E / β-thalassemia (β-thalassemia with mutation and / or multiplication of α-globin was allowed. [b] RBC transfusions and iron chelation therapy to maintain each patient's baseline hemoglobin level. [c] The trial is fully enrolled and patients continue to receive treatment or follow-up.
BSC, best supportive care; RBC, red blood cell; s.c., subcutaneously.

Cappellini MD et al. N Engl J Med 2020;382:1219-1231.

BELIEVE trial endpoints

Primary endpoint:

- ≥ 33% reduction from baseline in RBC transfusion burden (with a reduction of ≥ 2 RBC units) during Weeks 13–24

Key secondary endpoints:

- ≥ 33% reduction from baseline in RBC transfusion burden during Weeks 37–48
- ≥ 50% reduction from baseline in RBC transfusion burden during Weeks 13–24
- ≥ 50% reduction from baseline in RBC transfusion burden during Weeks 37–48
- Mean change from baseline in RBC transfusion burden during Weeks 13–24

Additional endpoint:

- ≥ 33% or ≥ 50% reduction from baseline in RBC transfusion burden during any 12 or 24 weeks on study

Cappellini MD et al. N Engl J Med 2020;382:1219-1231.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

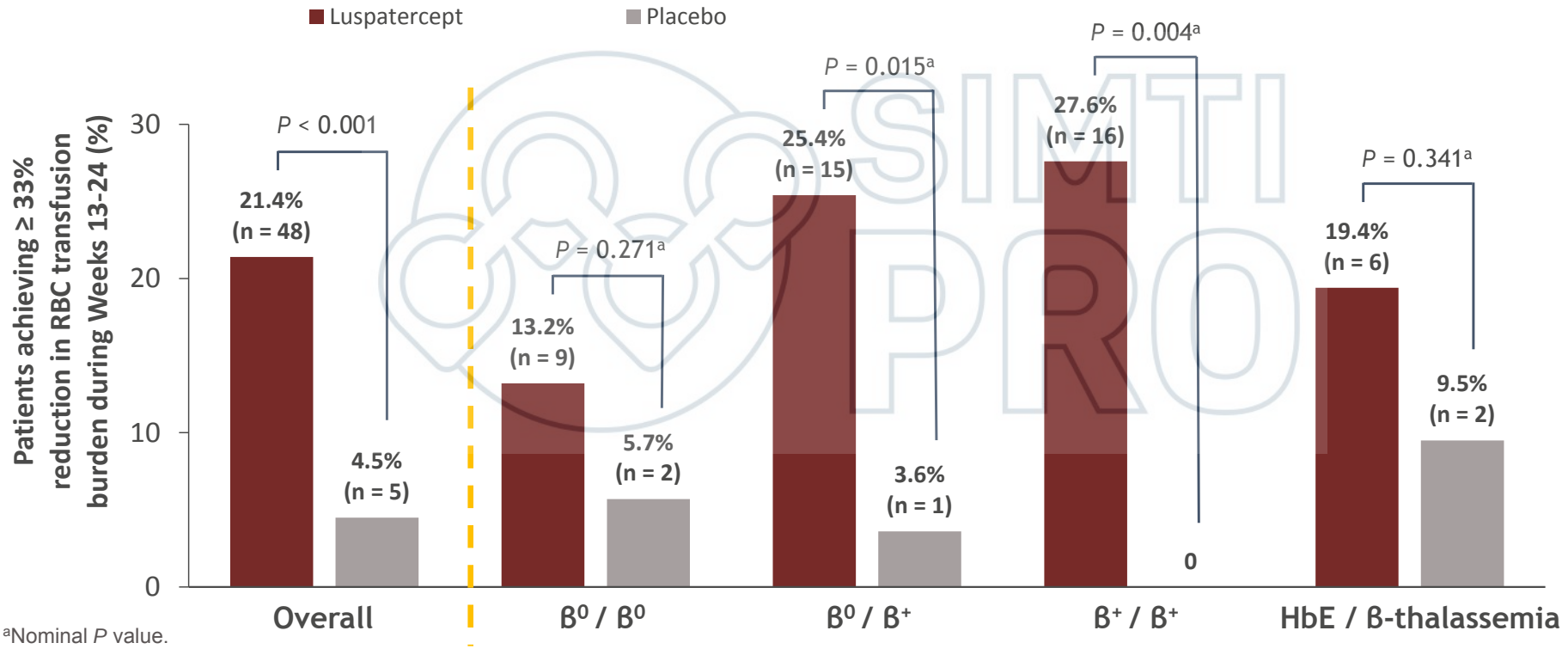
A Phase 3 Trial of Luspatercept in Patients with Transfusion-Dependent β-Thalassemia

N ENGL J MED 382;13 NEJM.ORG MARCH 26, 2020

M.D. Cappellini, V. Viprakasit, A.T. Taher, P. Georgiev, K.H.M. Kuo, T. Coates, E. Voskaridou, H.-K. Liew, I. Pazgal-Kobrowski, G.L. Forni, S. Perrotta, A. Khelif, A. Lal, A. Kattamis, E. Vlachaki, R. Origa, Y. Aydinok, M. Bejaoui, P.J. Ho, L.-P. Chew, P.-C. Bee, S.-M. Lim, M.-Y. Lu, A. Tantiworawit, P. Ganeva, L. Gercheva, F. Shah, E.J. Neufeld, A. Thompson, A. Laadem, J.K. Shetty, J. Zou, J. Zhang, D. Miteva, T. Zinger, P.G. Linde, M.L. Sherman, O. Hermine, J. Porter, and A. Piga, for the BELIEVE Investigators*

Achievement of ≥ 33% reduction in RBC transfusion burden during Weeks 13-24 (according to genotype)

A greater proportion of luspatercept-treated patients achieved ≥ 33% reduction from baseline in RBC transfusion burden during Weeks 13-24 versus placebo, regardless of β-globin genotype



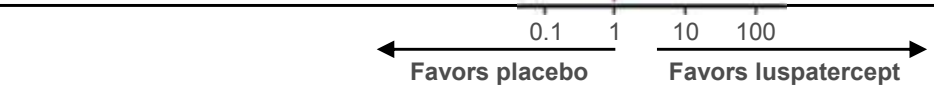
[a]Nominal *P* value.
Data cutoff: May 11, 2018.

BELIEVE trial

BELIEVE Trial

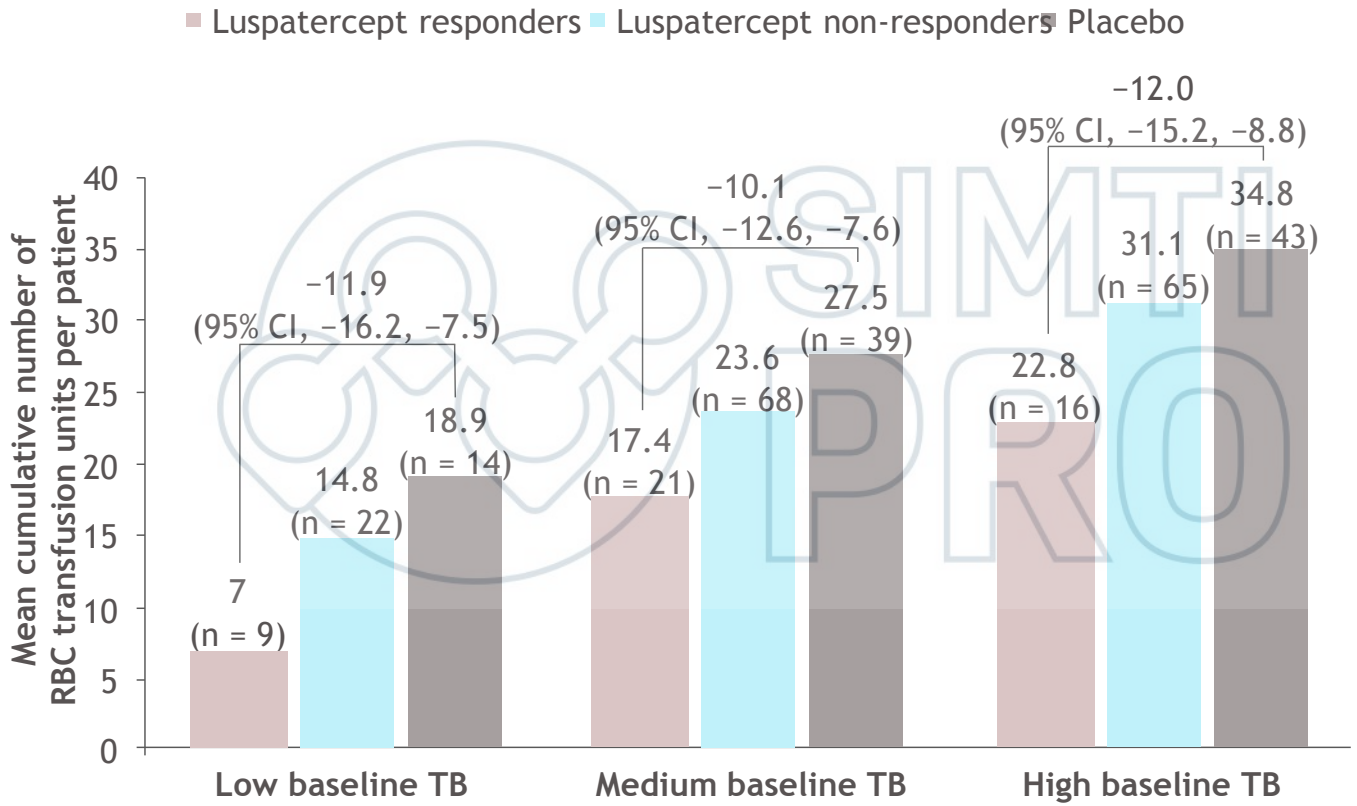
Primary endpoint: Subgroup analysis favors luspatercept

Sub-groups	Luspatercept n/N (%)	Placebo n/N (%)	OR (95% CI)	*P* value
Overall	48/224 (21.4)	5/112 (4.5)	5.79 (2.24, 14.97)	< 0.0001
Region: North America & Europe	23/100 (23.0)	1/51(2.0)	14.94 (1.95, 114.12)	0.0009
Region: Middle East & North Africa	11/52 (21.2)	2/26 (7.7)	3.22 (0.66, 15.77)	0.1351
Region: Asia–Pacific	14/72 (19.4)	2/35 (5.7)	3.98 (0.85, 18.62)	0.0629
Age: ≤ 32 years	22/129 (17.1)	4/63 (6.3)	3.00 (0.98, 9.20)	0.0476
Age: > 32 years	26/95 (27.4)	1/49 (2.0)	17.50 (2.27, 134.98)	0.0004
Splenectomy: Yes	31/129 (24.0)	2/65 (3.1)	9.72 (2.22, 42.53)	0.0003
Splenectomy: No	17/95 (17.9)	3/47 (6.4)	2.94 (0.81, 10.69)	0.0918
Sex: Female	35/132 (26.5)	4/63 (6.3)	5.33 (1.80, 15.80)	0.0011
Sex: Male	13/92 (14.1)	1/49 (2.0)	8.05 (1.01, 64.16)	0.0218
β-thalassemia Gene: β^0/β^0	9/68 (13.2)	2/35 (5.7)	2.54 (0.48, 13.51)	0.2708
β-thalassemia Gene: Non-β^0/β^0	39/155 (25.2)	3/77 (3.9)	8.35 (2.47, 28.23)	< 0.0001
Baseline Transfusion Burden: ≤ 6 units/12 weeks	27/112 (24.1)	3/56 (5.4)	5.61 (1.60, 19.65)	0.0033
Baseline Transfusion Burden: > 6 units/12 weeks	21/112 (18.8)	2/56 (3.6)	6.16 (1.38, 27.44)	0.0082
Baseline Hemoglobin: < 9 g/dL	22/87 (25.3)	4/51 (7.8)	3.78 (1.25, 11.42)	0.0128
Baseline Hemoglobin: ≥ 9 g/dL	26/137 (19.0)	1/61 (1.6)	14.17 (1.85, 108.79)	0.0012
Baseline Liver Iron: ≤ 3 mg/g dry weight	12/70 (17.1)	1/37 (2.7)	7.18 (0.88, 58.63)	0.0335
Baseline Liver Iron: > 3 to ≤ 7 mg/g dry weight	13/51 (25.5)	0/30 (0)	Infinity	0.0053
Baseline Liver Iron: > 7 to ≤ 15 mg/g dry weight	10/38 (26.3)	1/19 (5.3)	5.41 (0.67, 43.34)	0.0741
Baseline Liver Iron: > 15 mg/g dry weight	13/65 (20.0)	3/26 (11.5)	1.79 (0.47, 6.78)	0.3831



The BELIEVE Trial studied adult patients.

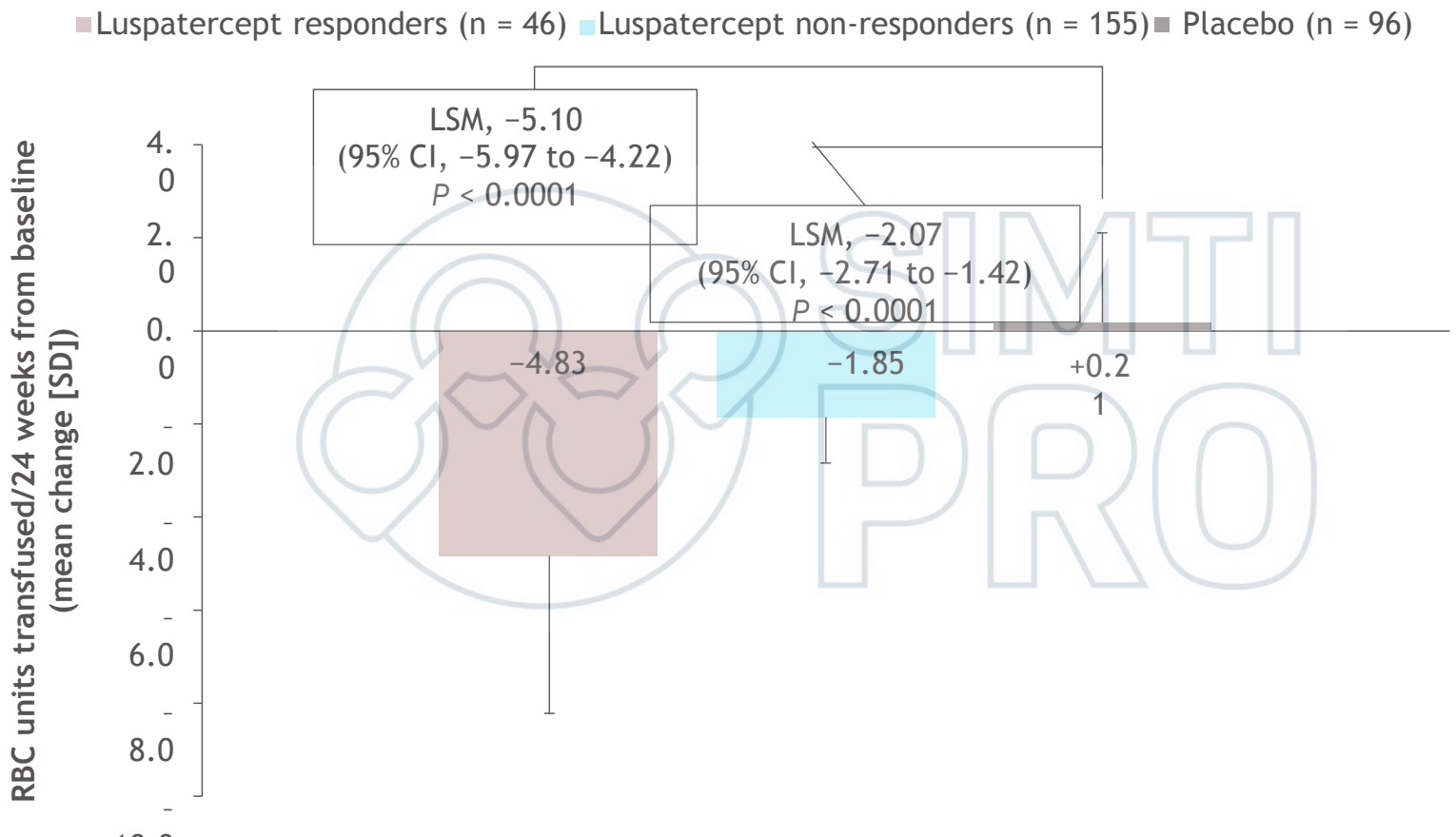
Mean cumulative number of RBC transfusion units by level of baseline TB through week 48



Baseline low, medium, and high TB were defined as receipt of ≤ 10, > 10 to ≤ 15, and > 15 RBC units/24 weeks, respectively.

BELIEVE

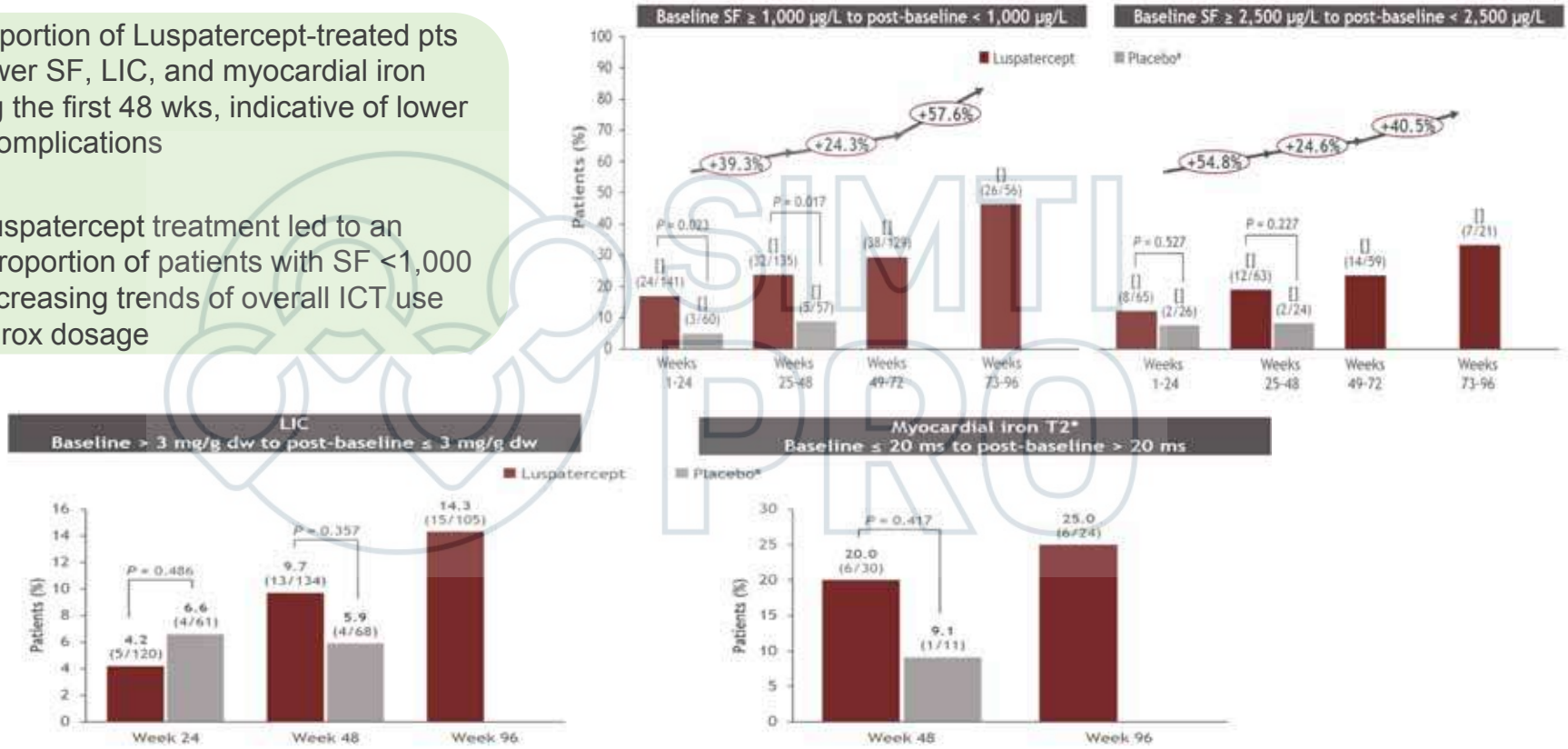
Mean change in RBC units transfused during weeks 25–48



LSM is luspatercept − placebo. Estimates are based on ANCOVA model with geographic regions defined at randomization and baseline TB as covariates.
SD, standard deviation.

Longitudinal effect of luspatercept on iron overload and iron chelation therapy

- A higher proportion of Luspatercept-treated pts shifted to lower SF, LIC, and myocardial iron levels during the first 48 wks, indicative of lower risk of IOL complications
- Long-term luspatercept treatment led to an increasing proportion of patients with SF <1,000 µg/L and decreasing trends of overall ICT use and deferasirox dosage



P values are estimated from Cochran–Mantel–Haenszel test. Patients with LIC ≥ 3 mg/g dw are considered to have iron overload. Myocardial iron T2* < 20 ms indicates increased cardiac risk. [a]Placebo patients evaluated up to Week 48.

Hermine O et al. Blood 2021;136:Presentation 1697.

BELIEVE Trial

Safety Summary

Treatment-Emergent Adverse Events, n (%)	Luspatercept (n = 223[a])	Placebo (n = 109[a])
Patients with at least 1 TEAE (any grade)	214 (96.0)	101 (92.7)
Patients with at least 1 grade TEAE (grade ≥ 3)[b]	65 (29.1)	17 (15.6)
Patients with at least 1 serious TEAE[c]	34 (15.2)	6 (5.5)
Patients with at least 1 TEAE resulting in the following:		
Death[d]	0	1 (0.9)
Study drug discontinuation	12 (5.4)	1 (0.9)

[a] Safety population. [b] No one organ class or system was predominant.[c] Anemia was the only serious TEAE occurring in > 1% of patients in either arm (luspatercept, n = 3 [1.4%]; placebo, n = 0 [0%]). [d] TEAE of acute cholecystitis resulted in death in 1 of 109 (0.9%) placebo patients; no luspatercept-treated patients died due to TEAEs. TEAE, treatment-emergent adverse event.
The BELIEVE Trial studied adult patients.

BELIEVE Trial

TEAEs by frequency ≥ 10% in Either Arm (all grades)

n (%)	Luspatercept (n = 223[a])	Placebo (n = 109[a])
Back pain	61 (27.4)	32 (29.4)
Upper respiratory tract infection	59 (26.5)	36 (33.0)
Headache	58 (26.0)	26 (23.9)
Bone pain	**44 (19.7)**	**9 (8.3)**
Arthralgia	**43 (19.3)**	**13 (11.9)**
Pyrexia	36 (16.1)	23 (21.1)
Cough	32 (14.3)	12 (11.0)
Fatigue	30 (13.5)	14 (12.8)
Oropharyngeal pain	28 (12.6)	12 (11.0)
Diarrhea	27 (12.1)	11 (10.1)
Dizziness	**25 (11.2)**	**5 (4.6)**
Asthenia	22 (9.9)	11 (10.1)
Myalgia	22 (9.9)	11 (10.1)
Pharyngitis	20 (9.0)	13 (11.9)

[a] Safety population.

The BELIEVE Trial studied adult patients.

BELIEVE Trial

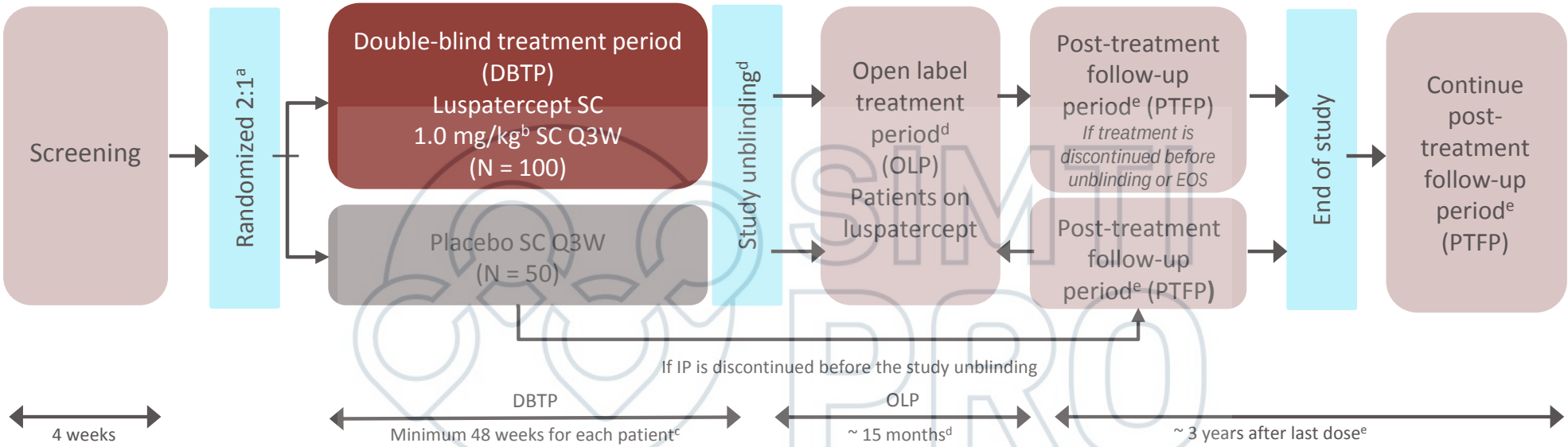
Grade 3–4 TEAEs by frequency ≥ 1% in Either Arm

n (%)	Luspatercept (n = 223[a])	Placebo (n = 109[a])
Anemia	7 (3.1)	0
Increased LIC	6 (2.7)	1 (0.9)
Hyperuricemia	6 (2.7)	0
Hypertension	4 (1.8)	0
Syncope	4 (1.8)	0
Back pain	3 (1.3)	1 (0.9)
Bone pain	3 (1.3)	0
Blood uric acid increased	3 (1.3)	0
Increased AST	3 (1.3)	0
Increased ALT	2 (0.9)	3 (2.8)
Thromboembolic events[b]	2 (0.9)	0

In total, thromboembolic events (all grades) were reported in **8/223 (3.6%)** luspatercept-treated patients (deep venous thrombosis, pulmonary embolism, portal vein thrombosis, ischemic stroke, thrombophlebitis, superficial phlebitis) and 1/109 (0.9%) placebo-treated patients (phlebitis). In all cases, patients had multiple risk factors for thromboembolic events

[a] Safety population. [b] Thromboembolic events included as a TEAE of interest; other events occurring in < 1% of patients are not shown.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.
The BELIEVE Trial studied adult patients.

Phase II RCT trial of luspatercept in adults with NTDT: The BEYOND trial



Primary endpoint

- Achievement of ≥ 1.0 g/dL mean Hb increase from baseline over a continuous 12-week interval during weeks 13–24 in the absence of RBC transfusions

Key secondary endpoint

- Mean change from baseline in NTDT-PRO T/W domain score over a continuous 12-week interval during weeks 13–24

Taher AT et al. EHA 2021; Presentation Number S101.

Study endpoints

Primary endpoint

- Achievement of ≥ 1.0 g/dL mean Hb increase from baseline over a continuous 12-week interval during weeks 13–24 in the absence of RBC transfusions

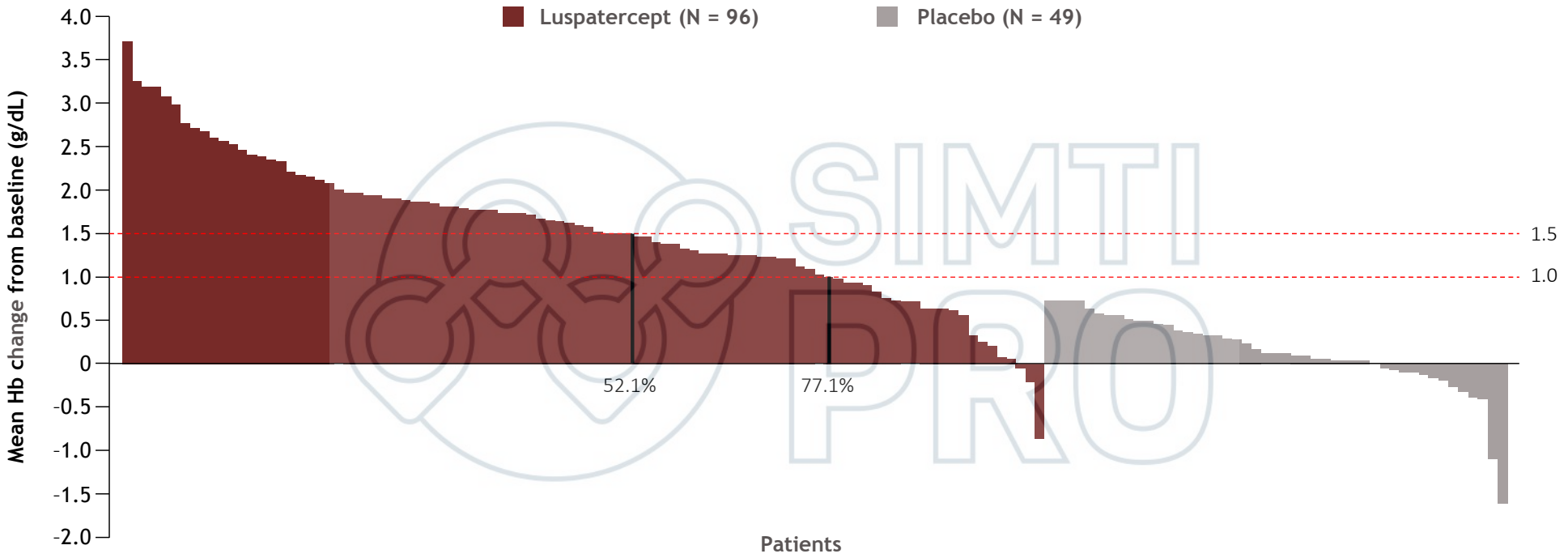
Key secondary endpoint

- Mean change from baseline in NTDT-PRO T/W domain score over a continuous 12-week interval during weeks 13–24

Secondary endpoints

- Achievement of ≥ 1.5 g/dL mean Hb increase from baseline over a continuous 12-week interval during weeks 13–24 in the absence of RBC transfusions
- Proportion of patients who remained RBC transfusion-free over 24 weeks
- Mean change in NTDT-PRO T/W domain score by visit
- Achievement of ≥ 1.0 g/dL mean Hb increase from baseline over a continuous 12-week interval during weeks 37–48 in the absence of RBC transfusions
- Duration of the mean Hb increase from baseline ≥ 1.0 g/dL during any 12-week interval
- Safety and tolerability of luspatercept

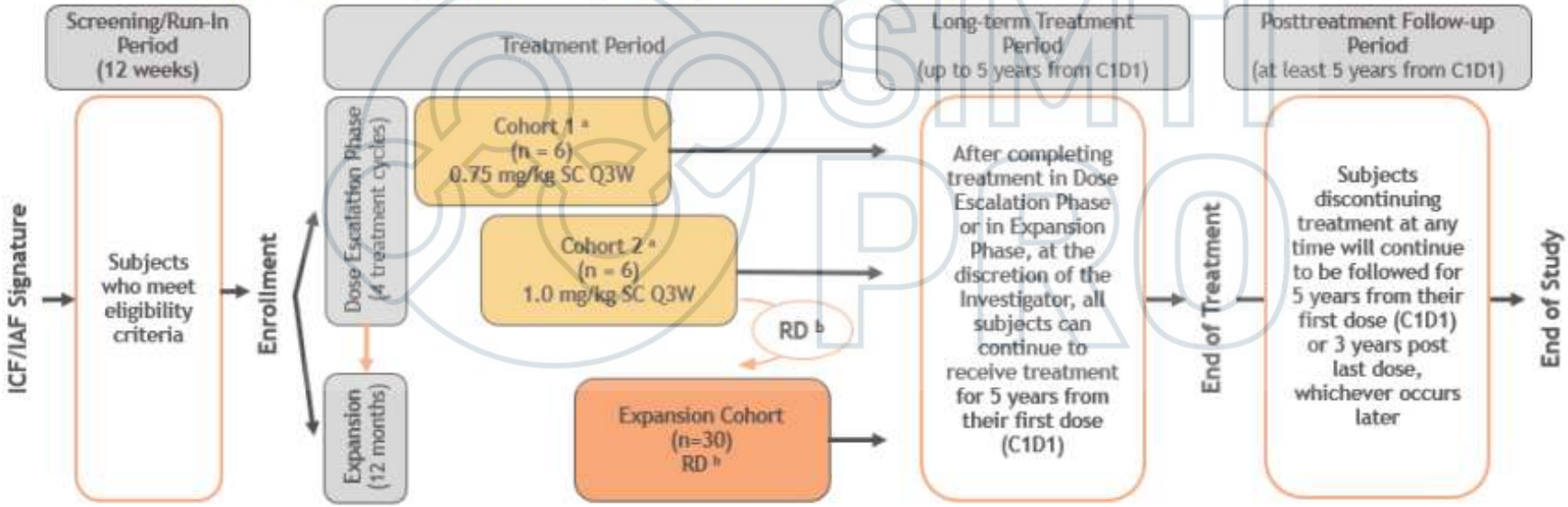
Mean Hb change from baseline during weeks 13–24



- During weeks 13–24, 50 (52.1%) patients in the luspatercept arm achieved a mean Hb increase of ≥ 1.5 g/dL from baseline

A PHASE 2A STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF LUSPATERCEPT (ACE-536) IN PEDIATRIC SUBJECTS WHO REQUIRE REGULAR RED BLOOD CELL TRANSFUSIONS DUE TO BETA (β)-THALASSEMIA

Overall Study Design - Part A: Age Group 12 to < 18 Years Old



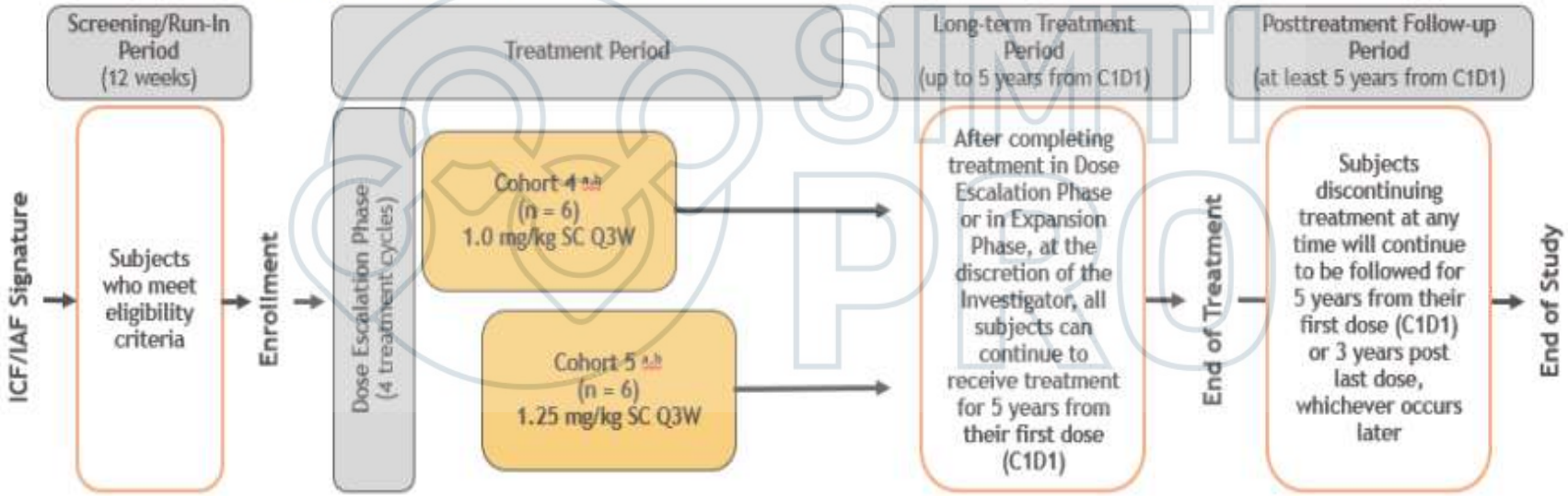
C1D1 = Cycle 1 Day 1; IAF = informed assent form; ICF = informed consent form; Q3W = every 3 weeks (21 days); RD = recommended dose; SC = subcutaneous.

[a] Dose Review Team to determine whether or not to enroll Cohort 2 at the next planned dose level.

[b] Expansion Cohort will be initiated after RD has been established by Dose Review Team.

A PHASE 2A STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF LUSPATERCEPT (ACE-536) IN PEDIATRIC SUBJECTS WHO REQUIRE REGULAR RED BLOOD CELL TRANSFUSIONS DUE TO BETA (β)-THALASSEMIA

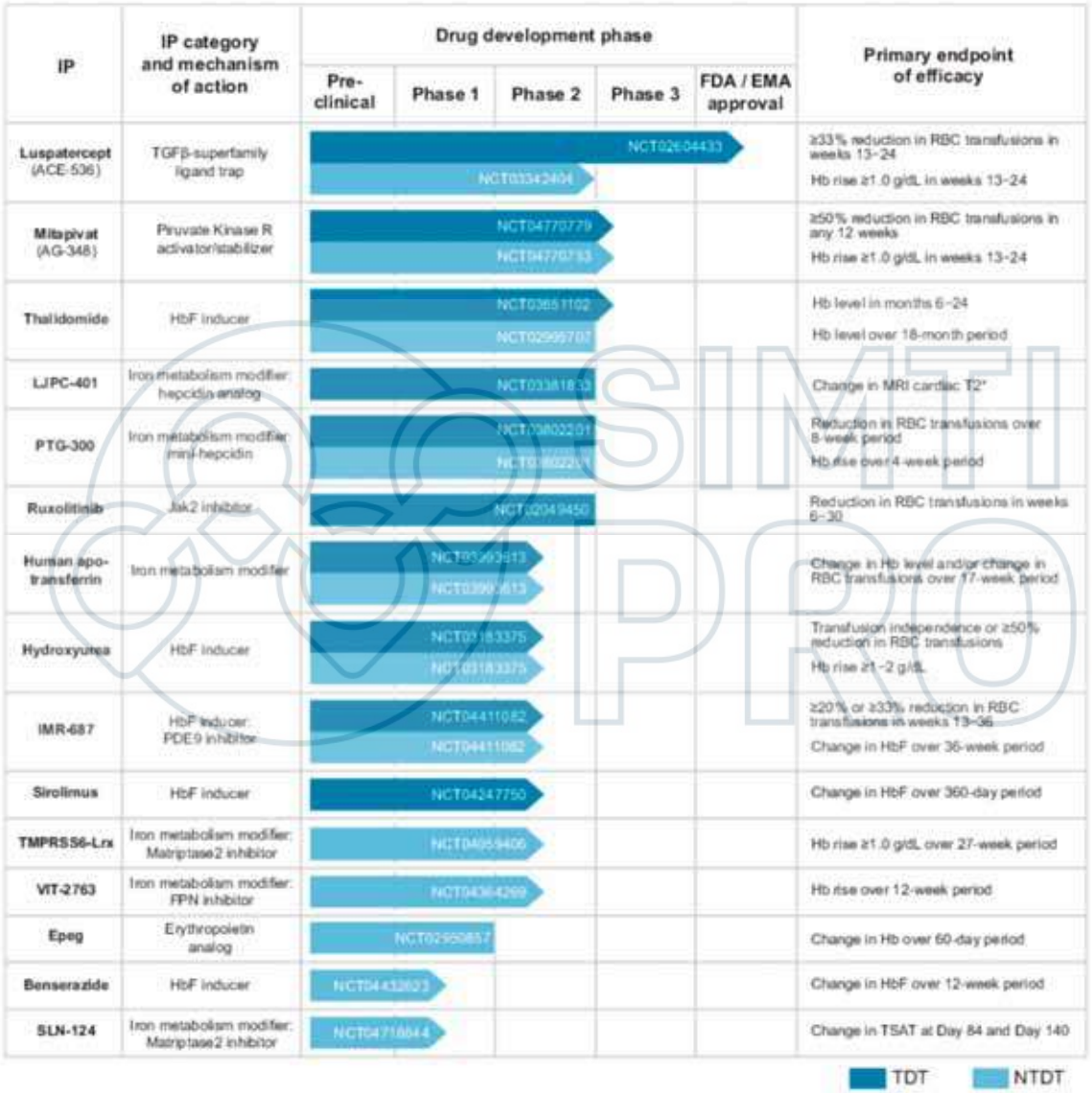
Overall Study Design - Part B: Age Group 6 to < 12 Years Old



C1D1 = Cycle 1 Day 1; DMC = Data Monitoring Committee; EMA = European Medicines Agency; IAF = informed assent form; ICF = informed consent form; Q3W = every 3 weeks (21 days); SC = subcutaneous, SSC = Scientific Steering Committee.

[a] Dose Review Team to determine whether or not to enroll Cohort 5 at the next planned dose level.

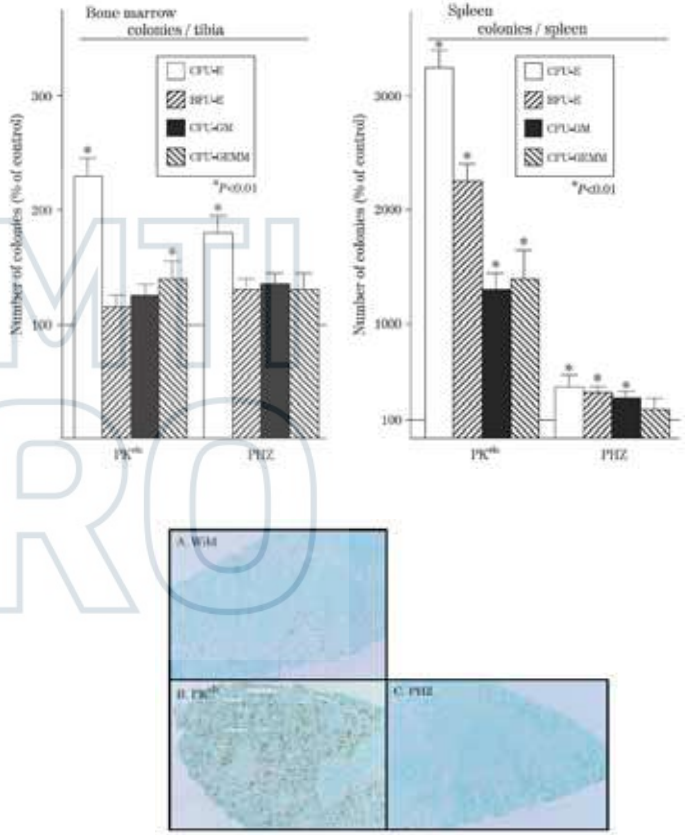
[b] Part B (age group: 6 to < 12 years) to be initiated as per DMC's recommendation based on the overall data collected during the Treatment Period of Part A (age group: 12 to < 18 years old). The DMC's recommendation is to be shared with the SSC and the EMA.



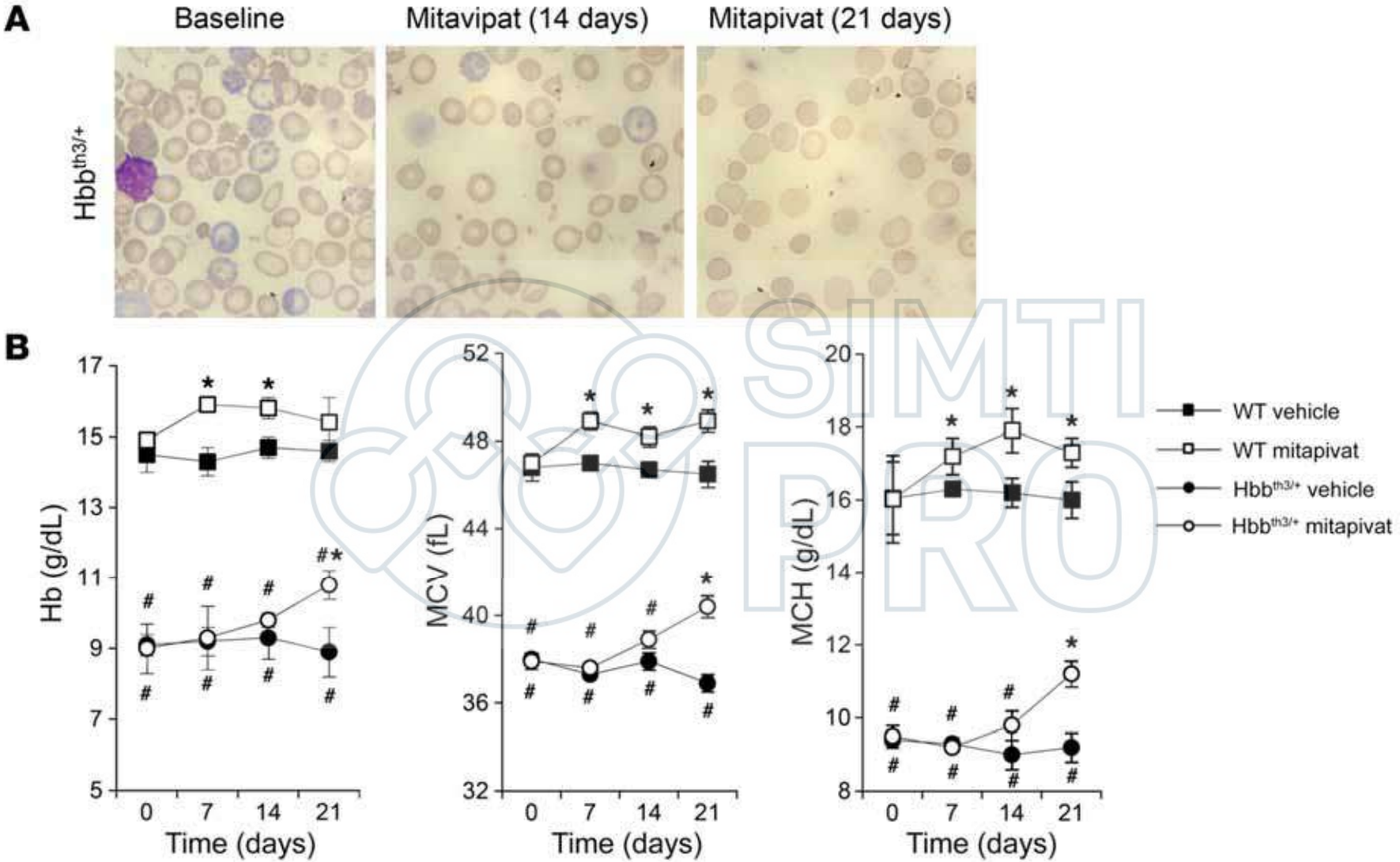
Longo F, *IJMS*, 2021

Mitapivat (PK activator)

- Metabolic disturbance in PK deficiency alters not only the survival of RBCs but also the maturation of erythroid progenitors, resulting in ineffective erythropoiesis. ATP supply appears to be insufficient in thalassemic RBCs to maintain membrane fitness and clearance of globin precipitates
- Mitapivat (AG-348) is a first-in-class oral, small-molecule, allosteric activator of the RBC-specific form of PK (PK-R)
- Mitapivat has already shown efficacy and safety in clinical trials of patients with PK deficiency
- In mouse models β-thalassemia, mitapivat increased ATP levels, reduced markers of ineffective erythropoiesis, and improved anemia, RBC survival, and indexes of iron overload



Aizawa S *et al. Exp Hematol* 2005;33:1292-1298; Yang H *et al. Clin Pharmacol Drug Dev* 2019;8:246-259; Grace *RF et al. N Engl J Med* 2019;381:933-944; Matte A *et al. Haematologica* 2016;101:18(S135) (abs).



Matte A, *JCI*, 2021

Interim data from phase 2 trial

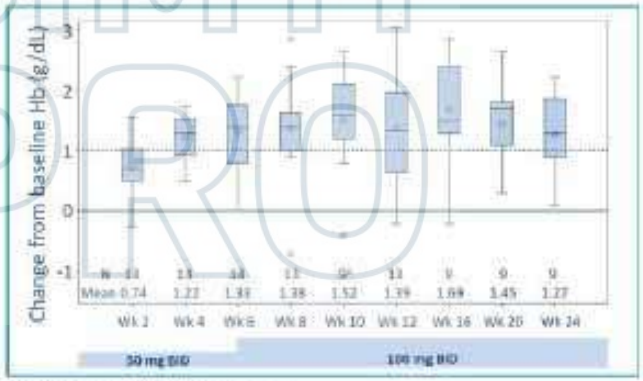
- Hb increase of ≥1.0 g/dL in 8 of 9 patients at 12 weeks with favorable changes in markers of erythropoiesis and hemolysis
- AEs occurring in >3 patients included insomnia, dizziness, cough, dyspepsia, fatigue, headache, nasal congestion, nausea, and upper respiratory tract infection

Table. Patient demographics and characteristics at baseline

Baseline characteristics	Total (N = 18)
Median (range) duration of treatment, weeks	20.6 (11–50.0)
Male/female, n	5/13
Age, median (range), years	43.5 (29–67)
Race, n (%)	
Asian	9 (50.0)
White	4 (22.2)
Native Hawaiian or other Pacific Islander	1 (5.6)
Other*	4 (22.2)
Thalassemia type, n (%)	
α	5 (27.8)
β	13 (72.2)
Hb, median (range), g/dL	8.43 (5.6–9.8)
Indirect bilirubin, median (range), mg/dL	1.17 (0.31–5.52)
Lactate dehydrogenase, median (range), U/L	249 (126–613)
Erythropoietin, median (range), mU/mL	70.5 (15–11,191

Hb, hemoglobin.
Splenectomy and prior transfusions were reported in 2 patients each at baseline.
*Includes patients who reported more than 1 category, and 1 not reported.

Figure. Hb change over time



BID, twice daily; Hb, hemoglobin; Wk, week.
Solid blue line indicates baseline, dashed blue line indicates Hb 1 g/dL above baseline. Boxes represent interquartile range, lines in boxes indicate medians, diamonds indicate means, whiskers and outliers (circles) calculated with Tukey's method.
*4 patients were not evaluated at Week 10 due to a protocol amendment eliminating this visit.

Kuo KHM *et al. Blood* 2020;136:2600 (abs).

Mitapivat (PK activator) trials

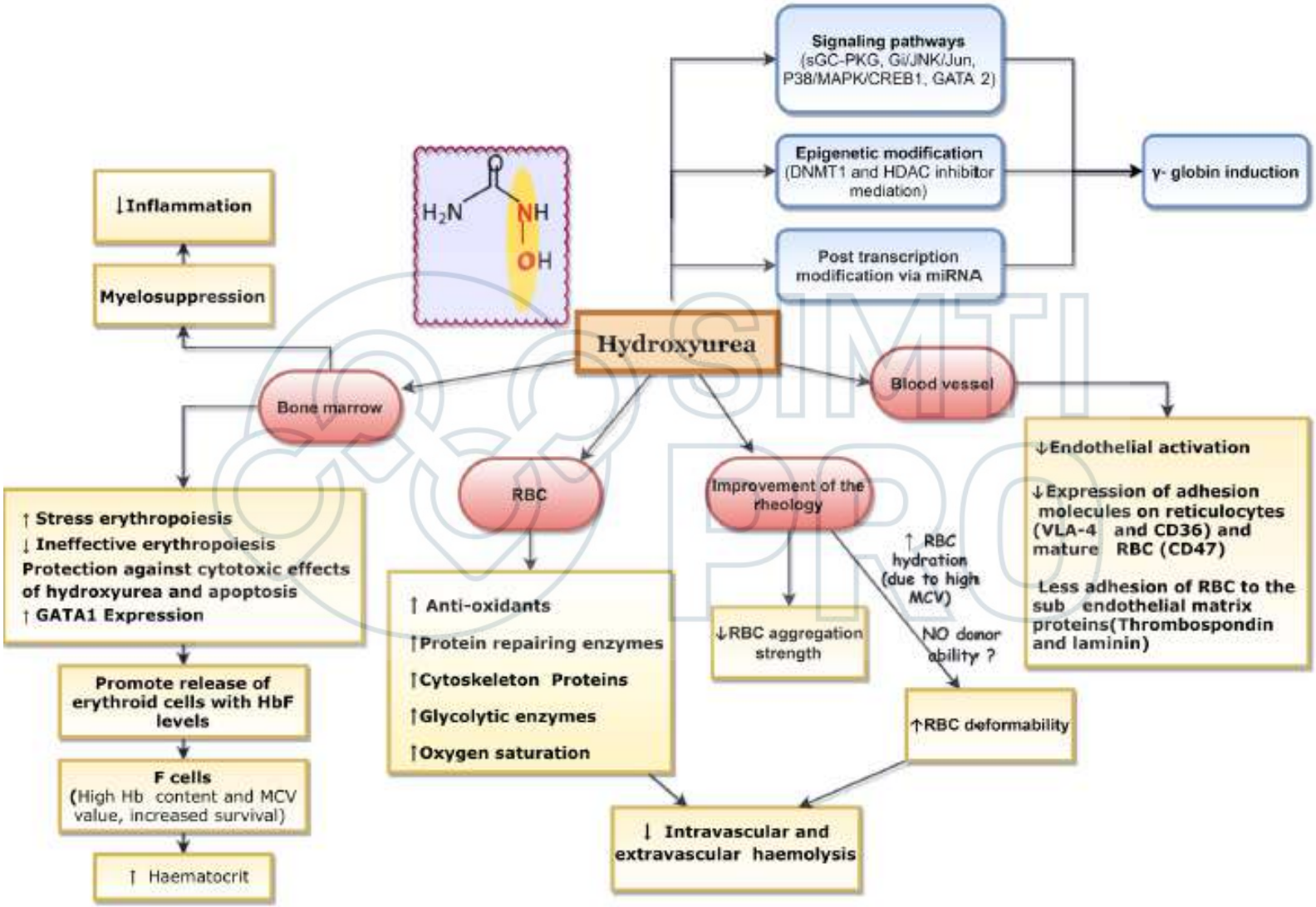
Agent	Clinical Trials*	Design	n‡, population, age	Key efficacy measures
PK activator				
Mitapivat (AG-348)	● NCT03692052 ● Active, not recruiting†	● Phase 2 ● Open-label	● n = 20 ● NTDT (including α-thalassemia) with Hb ≤10 g/dL ● ≥18 yr	● Hb increase ≥1 g/dL§ ● Hb, Reticulocytes, bilirubin, LDH, haptoglobin, ● EPO, nRBC, sTfR
	● ENERGIZE-T ● NCT04770779 ● Not yet recruiting	● Phase 3 ● Randomized, placebo-controlled, double-blind	● n = 240 ● TDT (including α-thalassemia) ● ≥18 yr	● Transfusion reduction (≥50%§, ≥33%) / ● independence ● Transfusion requirement ● SF, TSAT, TIBC
	● ENERGIZE ● NCT04770753 ● Not yet recruiting	● Phase 3 ● Randomized, placebo-controlled, double-blind	● n = 171 ● NTDT (including α-thalassemia) with Hb ≤10 g/dL ● ≥18 yr	● Hb increase ≥1 g/dL§ ● PRO ● Hb, Hb increase ≥1.5 g/dL ● Reticulocytes, bilirubin, LDH, haptoglobin, EPO, ● SF, TSAT

Musallam KM *et al. Am J Hematol* 2021;

Hb F inducers

Category	Examples of Inducers
Chemotherapeutic agents (ribonucleotide reductase inhibitors)	HU
Chemotherapeutic agents (DNA methyltransferase inhibitors)	5-Azacytidine, decitabine and citarabine
Short chain fatty acids and derivatives (histone deacetylase inhibitors)	Butyrates, tricostatin, apicidine, and scriptaid
DNA binding agents	Mithramycin, cisplatin and analogues, tallimustine and analogues, and angelicin
mTOR inhibitors	Rapamycin
Immunomodulatory drugs	Thalidomide, revlimid, and Pomalidomide
Cytokines	Erythropoietin (EPO), stem cell factor and TGF-β

Ng NY, Int Sch Res Notices, 2014



Yasara et al. Orphanet J Rare Dis (2021) 16:114

IP	IP category and mechanism of action	Drug development phase					Primary endpoint of efficacy
		Pre-clinical	Phase 1	Phase 2	Phase 3	FDA / EMA approval	
Thalidomide	HbF inducer			NCT03651102 NCT02395707			Hb level in months 6–24 Hb level over 18-month period
Hydroxyurea	HbF inducer			NCT03183375 NCT03183375			Transfusion independence or ≥50% reduction in RBC transfusions Hb rise ≥1–2 g/dL
IMR-687	HbF inducer: PDE9 inhibitor			NCT04411082 NCT04411082			≥20% or ≥33% reduction in RBC transfusions in weeks 13–36 Change in HbF over 36-week period
Sirolimus	HbF inducer			NCT04247750			Change in HbF over 360-day period
Benserazide	HbF inducer		NCT04432623				Change in HbF over 12-week period

TDT NTDT

Longo F, *IJMS*, 2021

blood advances

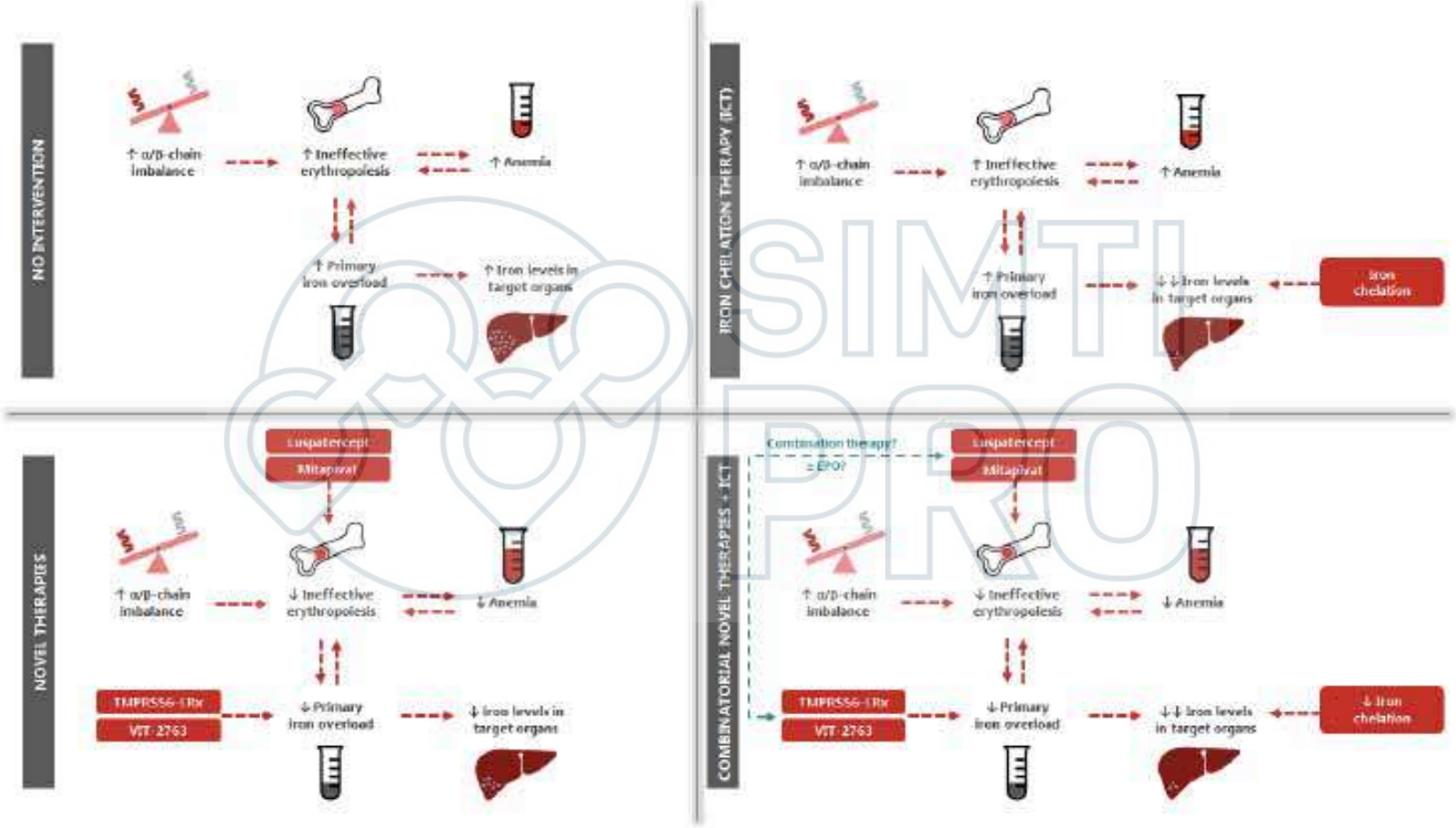
American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
bloodadvances@hematology.org

Evaluation of the combination therapy of hydroxyurea and thalidomide in β-thalassemia

Tracking no: ADV-2022-007031R2

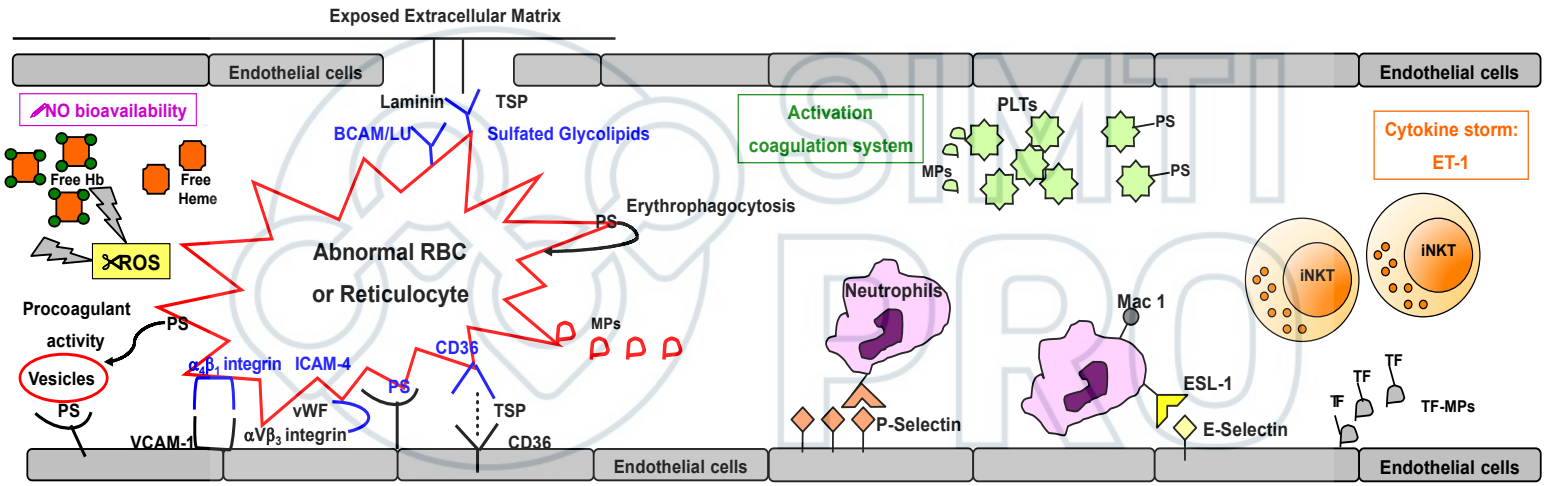
Saqib Ansari (Children's Hospital Karachi, Pakistan) Iqra Ansari (Dow University of Health Sciences, Pakistan) Misbah Wasim Munir (Children's Hospital Karachi, Pakistan) Amjad Sattar (Dow University of Health Sciences, Pakistan) Shariqa Khawaja (Children's Hospital Karachi, Pakistan) Muhammad Zohaib (Children's Hospital Karachi, Pakistan) Zeeshan Hussain (Children's Hospital Karachi, Pakistan) Syed Adil (Dow University of Health Sciences, Pakistan) Ali Ansari (Children's Hospital Karachi, Pakistan) Usman Ansari (Children's Hospital Karachi, Pakistan) Fawad Farooq (National Institute of Cardiovascular diseases, Pakistan) Noor-un-Nisa Masqati (Dow University of Health Sciences, Pakistan)

The path forward for NTDT: combination therapies?



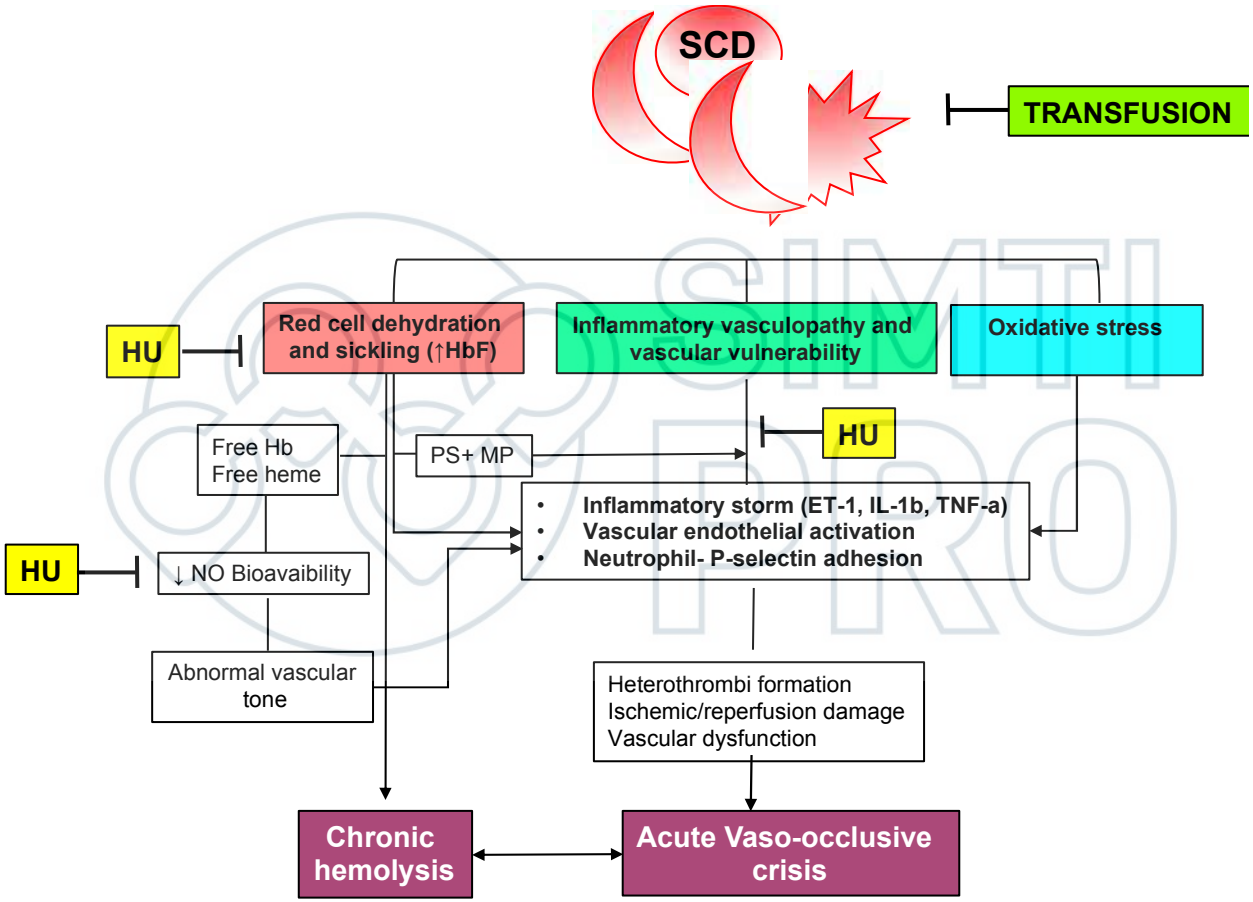
Musallam KM *et al. Am J Hematol* 2021;96:E57-E59.

The high Biocomplexity of SCD Substains Multi-Organ Damage

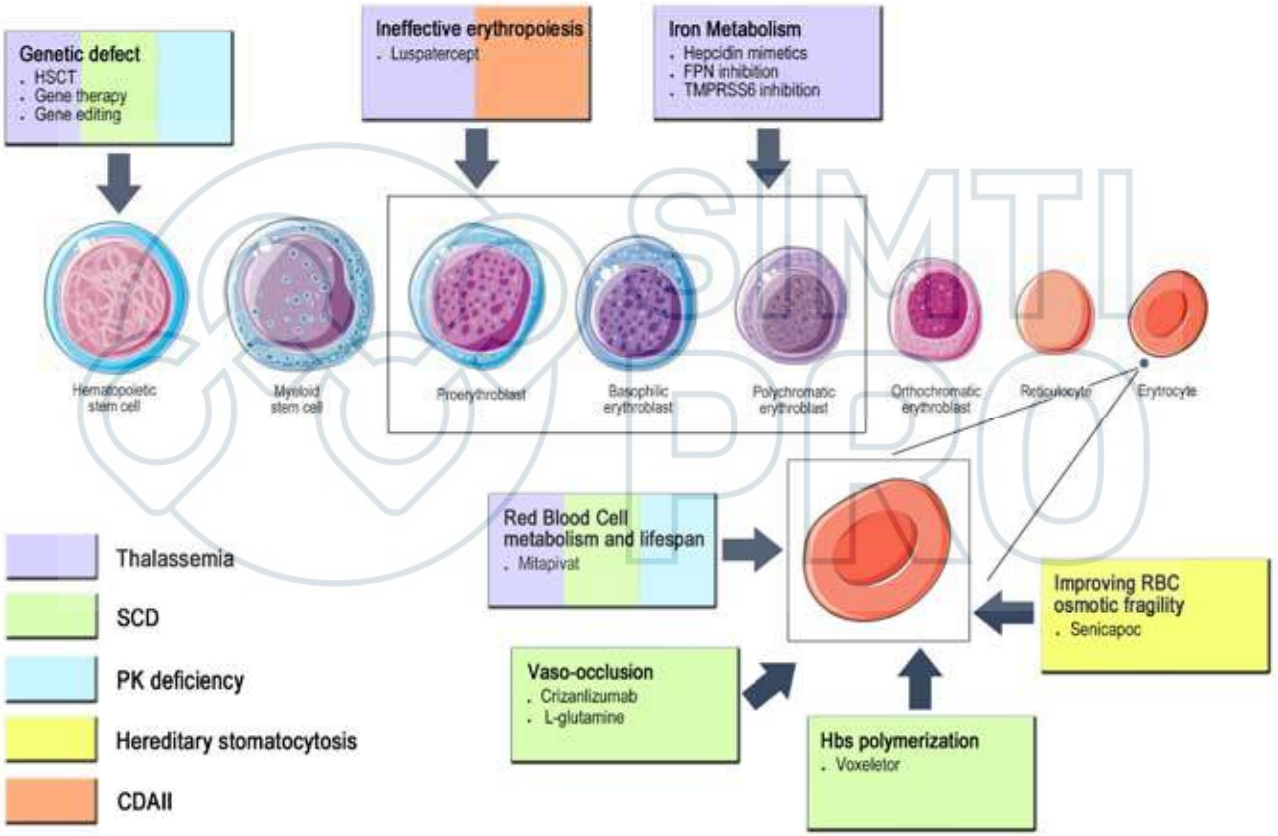


Modified from De Franceschi L *et al.* Seminars in Thrombosis, 37: 266; 2011

Gold-standard treatments of SCD

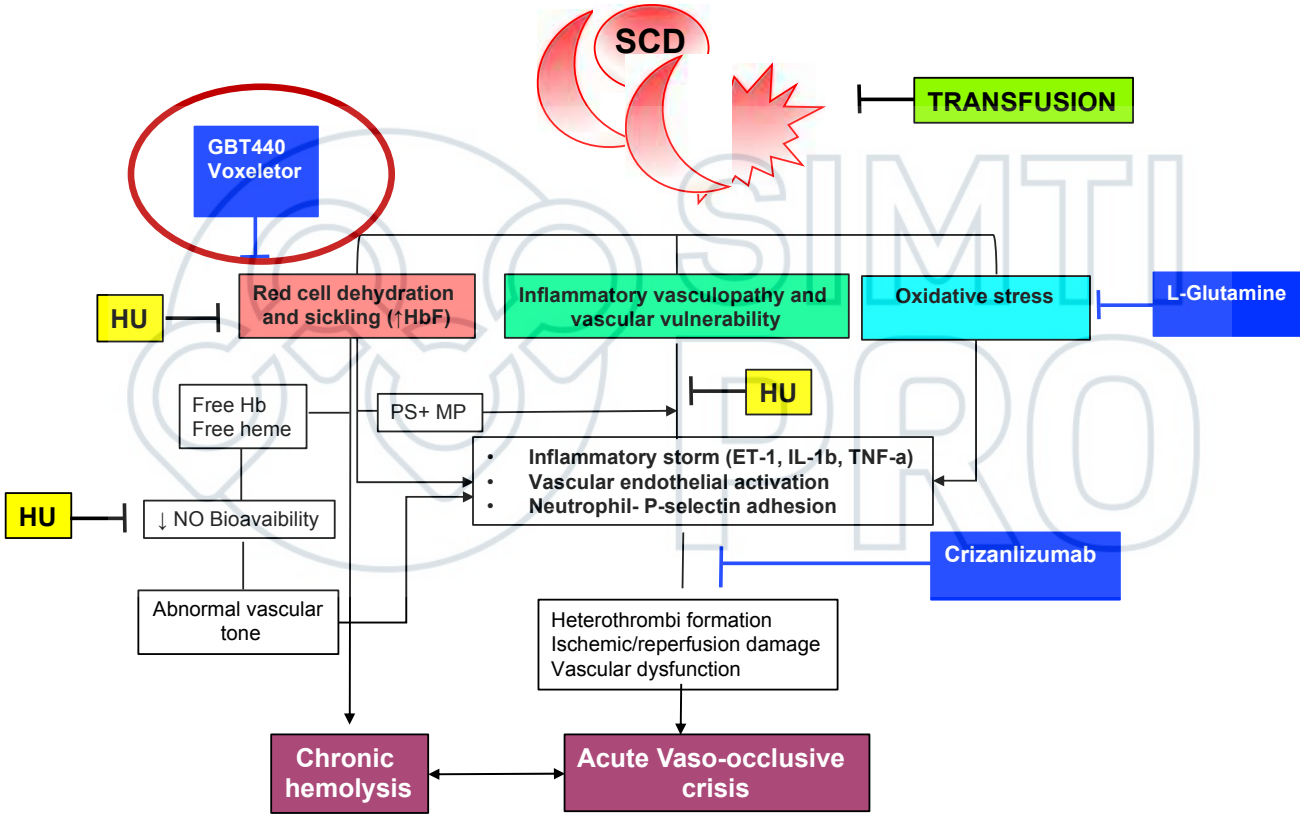


Emoglobinopatie: recenti approcci terapeutici



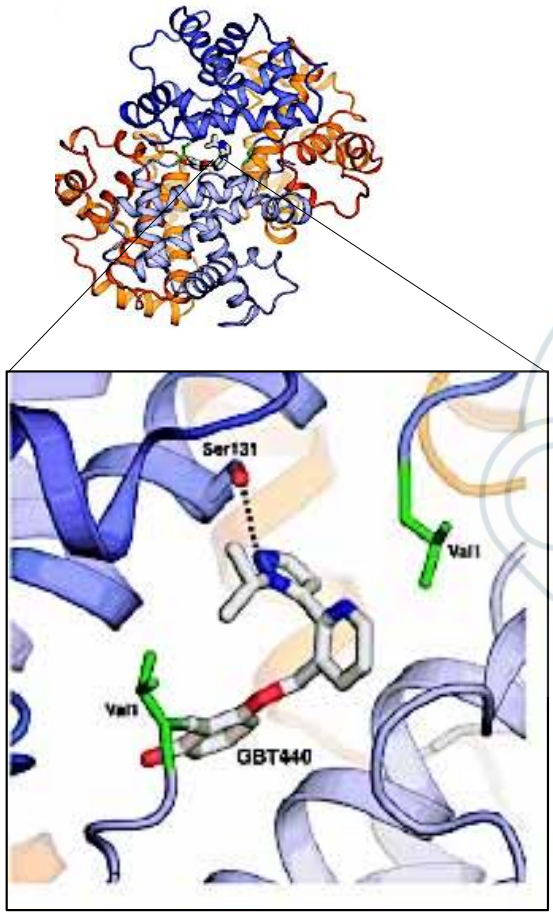
Cappellini MD, submitted

Pathophysiologic based new therapeutic options for SCD



De Franceschi L et al. Seminars in Thrombosis, 37: 266; 2011; De Franceschi L Haematologica 100 (S3): 195-7, 2015; Matte A et al Mediterr J Hematol Infect Disease 11: e2019002, 2019; Matte A et al Exp Opinion Invest Drug 29: 23-31, 2020

Voxeletor (GBT440): oral anti-sickling agent



- **Voxeletor** is an oral available potent and direct anti-sickling agent
- **Voxeletor** binds to HbS and promotes a left shift in p50 of HbS, **delaying HbS polymerization and sickling**

Dufu K et al. . Blood. 2014;124:217; Oder E et al. BJH 175: 24, 2016; Oksenberg D et al BJH 175: 141, 2016; Li Q et al PNAS 11: e689, 2017

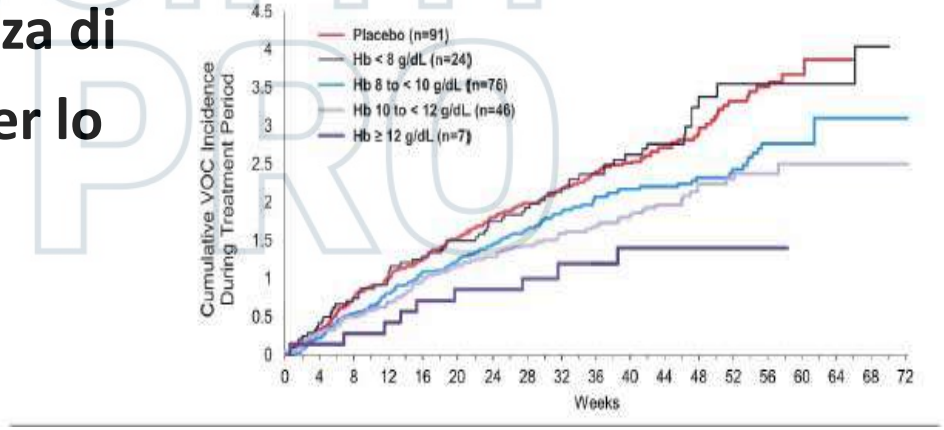
- **Studi di fase II in soggetti falcemici ha dimostrato un buon profilo di sicurezza e di tollerabilità per Voxeletor associato ad un miglioramento degli indici di emolisi ed una riduzione della reticolocitosi (#NCT02285088)**

- **L'agenzia del farmaco statunitense (FDA) ha definito Voxeletor come terapia rivoluzionaria per la drepanocitosi**

Oder E et al BJH 175: 24, 2016; Oksenberg D et al BJH 175: 141, 2016; Lehrer-Graiwer J et al Blood 126: 542, 2015; Washington C et al. EHA abstract # P620, 2017

Studio di fase III (HOPE, #NCT03036813)-studio placebo caso controllo doppio cieco multicentrico e multinazionale

- **Voxeletor 900-1500 mg/die periodo di osservazione ≥24 sett.**
- **Riduzione degli eventi VOC**
- **Aumento dei livelli di Hb in assenza di effetto viscosita' possibile rischio per lo sviluppo di VOCs**



Vichinsky E et al ASH 2019; abstract #2313

Combined treatment Voxeletor and HU

Table 1. Change in Laboratory Parameters from Baseline to Week 24

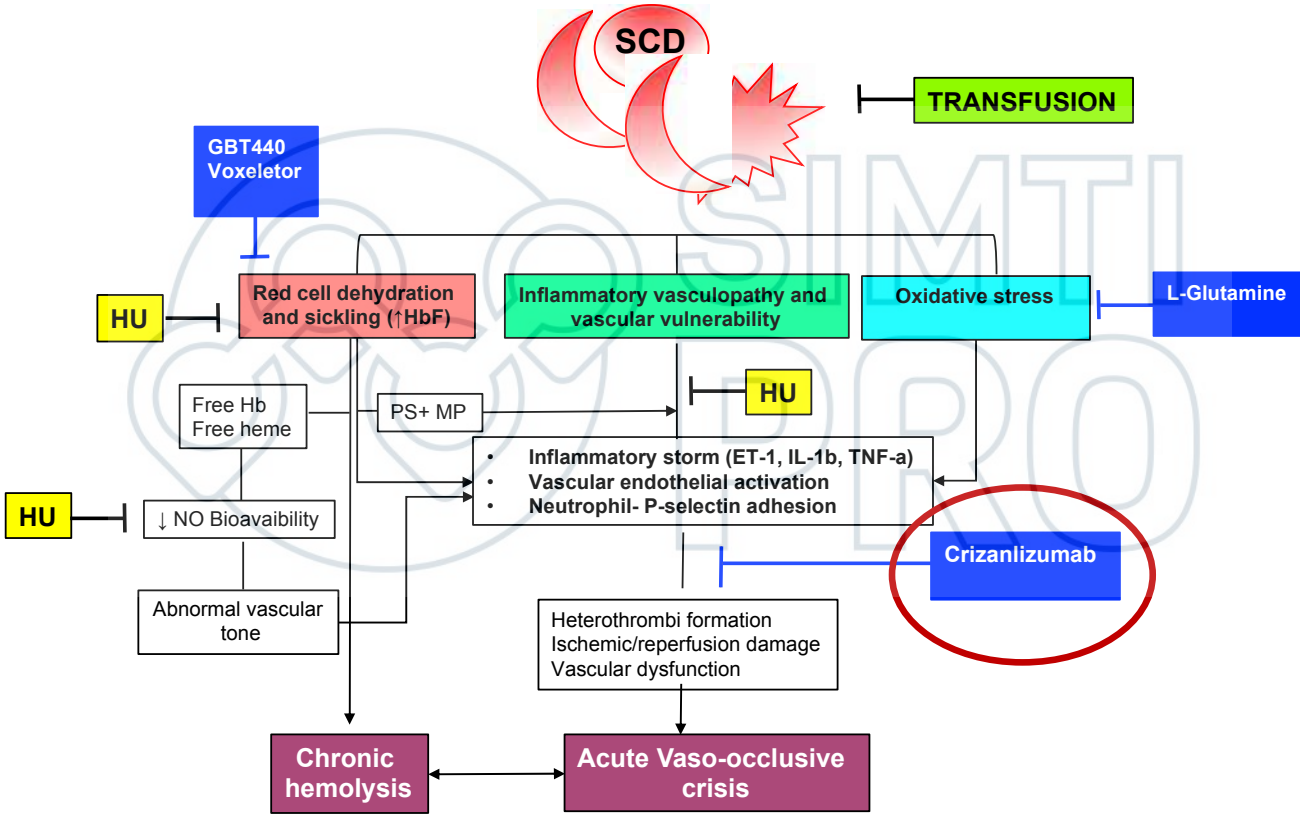
	Mean Change from Baseline (95% CI*) in Laboratory Parameters					
	Voxelotor 1500 mg		Voxelotor 900 mg		Placebo	
Hydroxyurea	Yes	No	Yes	No	Yes	No
Hb (g/dL) (n=229)	1.3 (1.0, 1.6)	1.3 (0.8, 1.8)	0.7 (0.5, 1.0)	0.8 (0.3, 1.3)	0.0 (-0.2, 0.2)	0.0 (-0.2, 0.3)
HbF (%) (n=131)	-1.8 (-3.1, -0.5)	0.2 (-0.9, 1.3)	-1.8 (-3.7, 0.1)	-0.7 (-1.1, -0.3)	-0.1 (-1.8, 1.5)	0.5 (0.0, 1.1)

SCD (1500 mg/d-> patient improvement evaluated by CGI-C (clinical global impression scale-change)

Hb, hemoglobin; HbF, fetal hemoglobin; MCV, mean corpuscular volume; RDW, red cell distribution width.

Russel W et al ASH 2019 abstract #1003; Smith WR et al ASH 2020, abstract# 802

Pathophysiologic based new therapeutic options for SCD

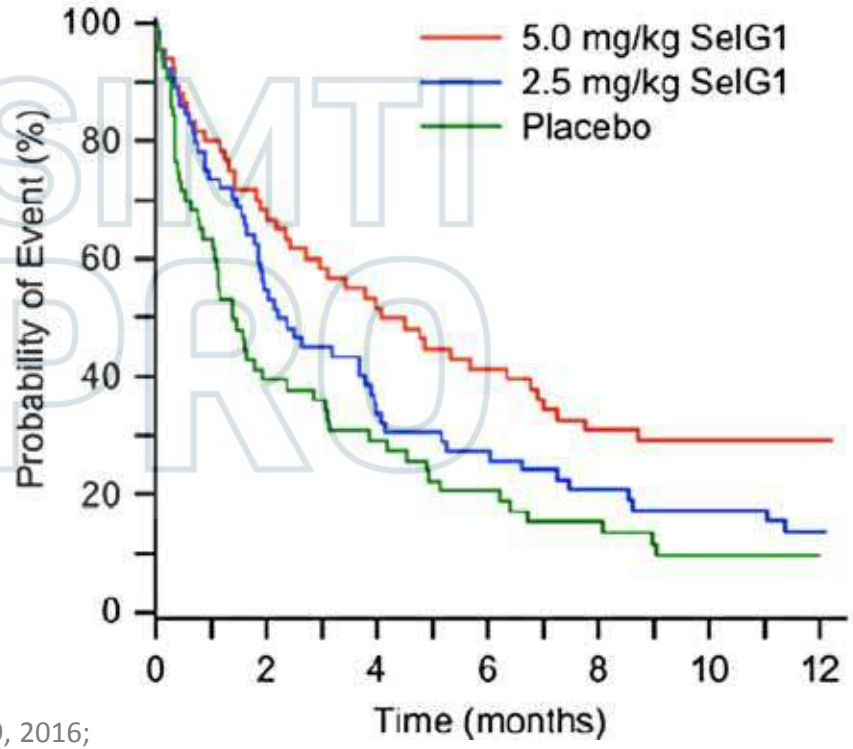


De Franceschi L et al. Seminars in Thrombosis, 37: 266; 2011; De Franceschi L Haematologica 100 (S3): 195-7, 2015; Matte A et al Mediterr J Hematol Infect Disease 11: e2019002, 2019; Matte A et al Exp Opinion Invest Drug 29: 23-31, 2020

Humanized Monoclonal Ab against P-selectin (SelG1)

In a double blind placebo-controlled mutinational trial:

- **was safe and well tollerated**
- **Induced a 1 month P-selectin block**
- **Reduced pain crisis**
- **Increased the time between pain crisis**



Mandarino D et al Blood 122: abstract 970, 2013; Telen MJ Blood 127: 810-19, 2016; Ataga KI et al abstract 1, 2016 (Dec 4); Ataga KI et al N Engl J Med 2017;376:429-439; Ataga KI et al. N Engl J Med 2017;376:1796.; Slomski A. JAMA 2017;317:798.

- **SUSTAIN: double blind placebo-controlled phase II study (NCT0185361) with P-selectin inhibitor-Crizanlizumab**

- **Genopyte: SS, SC, S/β0, S/β+**

- **66 pts on 2.5 mg/Kg every 4 weeks and 67 pts on 5 mg/Kg every 4 weeks**

- **Crizanlizumab (5 mg/Kg every 4):**
  - **increases the likelihood of SCD adult patients being sickle cell pain crisis free**
  - **is effective also in patients under HU**

Kutlar A et al Haematologica S454, 2017

SUSTAIN study: Crizanlizumab reduces days requiring opioid use

Results

SUSTAIN Per Protocol Population

- In the PP population of the SUSTAIN trial, the median annual VOCs with Crizanlizumab 5 mg/kg was significantly reduced by 52% compared with Placebo (median 1.04 vs. 2.18; p=0.02).[4]
- No baseline characteristics were significantly different between treatment arms of the SUSTAIN PP population (**Table 1**).

Table 1

Baseline Characteristic	Category	Crizanlizumab 5 mg/kg (n = 40)	Placebo (n = 41)	p-value
Age, n (%)	>25 years	29 (72.5%)	25 (61.0%)	0.387
	16 to 25 years	11 (27.5%)	16 (39.0%)	
Sex, n (%)	Female	22 (55.0%)	24 (58.5%)	0.923
	Male	18 (45.0%)	17 (41.5%)	
Genotype, n (%)	HbSS	27 (67.5%)	26 (63.4%)	0.878
	Other	13 (32.5%)	15 (36.6%)	
Hydroxyurea Usage, n (%)	No	19 (47.5%)	13 (31.7%)	0.220
	Yes	21 (52.5%)	28 (68.3%)	
Number of Crises[a], n (%)	2 to 4	31 (77.5%)	27 (65.9%)	0.360
	5 to 10	9 (22.5%)	14 (34.1%)	
Prior Opioid Records[a], n (%)	# records =0	24 (60.0%)	19 (46.3%)	0.313
	# records >0	16 (40.0%)	22 (53.7%)	
Prior Opioid Records[a], Mean (SD)	Not applicable	0.60 (0.84)	0.85 (0.99)	0.217

[a] In the 12 months prior

Results

Analysis of Parenteral Opioids

- For this analysis, only parenteral opioids were included, with two assumptions tested:
  1. All parenteral fixed doses were taken as prescribed
  2. Both parenteral fixed or PRN doses were taken as prescribed.
- Under both assumptions tested, the median annual rate of opioid days were lower for patients in the Crizanlizumab 5 mg/kg arm compared with patients in the Placebo arm (**Table 3**).
- The absolute difference ranged from 2.01 to 2.03 median days per year and the relative reduction ranged from 50% to 67%.
- The 2.01 fewer median annual opioid days for patients treated with Crizanlizumab 5 mg/kg compared to Placebo was statistically significant (p=0.0470).

Table 3

	Median Annualized Opioid Days (Min., Max)				
Assumption	**Crizanlizumab 5 mg/kg (n = 40)**	**Placebo (n = 41)**	**Abs. Diff.**	**Rel. Red.**	**MW p-value**
Fixed	0.99 (0, 30.5)	3.02 (0, 37.0)	2.03	67%	0.0740
Fixed & PRN	1.98 (0, 32.6)	3.99 (0, 37.0)	2.01	50%	0.0470

Abbreviations: Abs. Diff. = absolute difference; MW = Mann-Whitney; n = number; PRN = pro re nata (administration of medication is not scheduled) Rel. Red. = relative reduction.

Crizanlizumb SCD treated patients show a statistic significant 50% reduction in days per year on parental opioids compared to placebo group

Crizanlizumab: SUSTAIN and SOLANCE studies

- Humanized anti-P-Selectin antibody (SelG1-Crizanlizumab)
- 111 pts from SUSTAIN and SOLANCE trial (NCT03264989, on going adult open label PK/PD study) 5 mg/Kg/ month
- Genotype: SS/SC, 75% in HU
- **85% grade 1-2:** headache (15%), nausea (19%), backpain (15.3%)
- **45.9% experiences infection:** upper respiratory tract and urinary infection
- **No bleeding**

Kanter J et al ASH 2019, abstract #991

Possibili prospettive: terapia combinate-politerapia nella SCD

- **HU in combination with:**
  - **Chronic P-selectin blockade** (Ataga KI et al. abstract #1, 2016; Telen MJ et al doi 10.111/BJH14303, 2016)
  - **Nutritional/dietary supplementation** (i.e.: ω-3 fatty acid, Mg^{2+} supplementation) (Kalis B et al Haematologica 100:870-80, 2015; Daak AA et al. AJCN 97: 37, 2013; Hankins JS et al. BJH 140: 80, 2008)
  - **Anti-inflammatory agents** (Regadenoson) (Field JJ Blood 121: 3329, 2013; Field JJ Blood 122 abstract # 977, 2013)
- **Combination treatment without HU:**
  - **Anti-sickling agent(s) combined with P-selectin blockade** (Swift R et al abstract #121, 2016; Lehrer J et al. abstract #2488, 2016; Ataga KI et al. abstract #1, 2016; Telen MJ et al doi 10.111/BJH14303, 2016)
  - **Anti-sickling agent(s) and anti-inflammatory agents such as Regadenoson** (Swift R et al abstract #121, 2016; Lehrer J et al. abstract #2488, Field JJ Blood 121: 3329, 2013; Field JJ Blood 122 abstract # 977, 2013)

Table 1. Recently completed and ongoing studies targeting adhesion

Study title	Clinical trials #/Phase	Intervention	Status	Primary sponsor
Selectin inhibitors				
Study of GMI-1070 for the Treatment of Sickle Cell Pain Crisis	NCT01119833 Phase 2	GMI-1070 (rivipansel)	Complete	GlycoMimetics
Efficacy and Safety of Rivipansel (GMI-1070) in the Treatment of Vaso-Occlusive Crisis in Hospitalized Subjects With Sickle Cell Disease	NCT02187003 Phase 3	GMI-1070 (rivipansel)	Ongoing	Pfizer
Study to Assess Safety and Impact of SelG1 With or Without Hydroxyurea Therapy in Sickle Cell Disease Patients With Pain Crises	NCT01895361 Phase 2	SelG1	Ongoing	Selexys
Sevuparin Infusion for the Management of Acute VOC in Subjects With SCD	NCT02515838 Phase 2	Sevuparin	Ongoing	Dilaforette
β blockers				
Study of Propranolol as Anti-Adhesive Therapy in Sickle Cell Disease (SCD)	NCT01077921 Phase 2	Propranolol	Complete	Duke Univ.
Propranolol and Red Cell Adhesion in Non-asthmatic Children with Sickle Cell Disease	NCT02012777 Phase 1	Propranolol	Ongoing	Univ. of Miami
Other inhibitors of adhesion				
Phase III Randomized Study of Poloxamer 188 for Vaso-Occlusive Crisis of Sickle Cell Disease	NCT00004408 Phase 3	Poloxamer 188	Complete	Mast Therapeutics. CytRx
Evaluation of Purified Poloxamer 188 in Vaso-Occlusive Crisis of Sickle Cell Disease (EPIC)	NCT01737814 Phase 3	Poloxamer 188	Ongoing	Mast Therapeutics

Table 2. Recently completed and ongoing studies targeting inflammation

Study title	Clinical trials #/Phase	Intervention	Status	Primary sponsor
Adenosine and invariant NK T (iNKT) cells				
Adenosine 2A Agonist Lexiscan in Children and Adults With Sickle Cell Disease	NCT01085201 Phase 1	Regadenoson	Complete	Dana-Farber Cancer Institute
A Phase II Trial of Regadenoson in Sickle Cell Anemia	NCT01788631 Phase 2	Regadenoson	Ongoing	Dana-Farber Cancer Institute
Safety, Pharmacokinetic, and Pharmacodynamic Study of NKTT120 in Adult Patients With Stable Sickle Cell Disease (SCD)	NCT01783691 Phase 1	NKTT120	Complete	NKT Therapeutics
Leukotrienes				
Phase 2 Study of Montelukast for the Treatment of Sickle Cell Anemia	NCT01960413 Phase 2	Montelukast	Ongoing	Vanderbilt Univ.
Trial of Zileuton CR in Children and Adults With Sickle Cell Disease	NCT01136941 Phase 1	Zileuton	Complete	Children's Hospital Medical Center, Cincinnati
Neutrophil adhesion and non-specific anti-inflammatory reagents				
Intravenous Gammaglobulin for Sickle Cell Pain Crises	NCT01757418 Phase 1/2	IVIg	Ongoing	A. Einstein College of Medicine, Yeshiva Univ.
Effect of Simvastatin Treatment on Vaso-occlusive Pain in Sickle Cell Disease	NCT01702246 Phase 2	Simvastatin	Ongoing	Children's Hospital & Research Center Oakland

Table 3. Recently completed and ongoing studies of HbF induction and antisickling agents

Study title	Clinical trials #/Phase	Intervention	Status	Primary sponsor
HbF Induction				
Study of Decitabine and Tetrahydrouridine (THU) in Patients With Sickle Cell Disease	NCT01685515 Phase 1	Decitabine and Tetrahydrouridine	Ongoing	Cleveland Clinic
Decitabine for High-Risk Sickle Cell Disease	NCT01375608 Phase 2	Decitabine	Suspended	NIH Clinical Center, NHLBI
Phase II Randomized Trial:Arginine Butyrate Plus Standard Local Therapy in Patients With Refractory Sickle Cell Ulcers	NCT00004412 Phase 2	Arginine Butyrate	Complete	Boston Med Ctr
Phase 1 Placebo Controlled Study of the Safety, Activity and Pharmacokinetics of HQK-1001 in Healthy Subjects	NCT00717262 Phase 1	HQK-1001	Complete	HemaQuest
Phase 1/2 Study to Evaluate the Safety, Tolerability and Pharmacokinetics of HQK-1001 Administered Daily in Patients With Sickle Cell Disease	NCT00842088 Phase 1/2	HQK-1001	Complete	HemaQuest
A Study of HQK-1001 in Patients With Sickle Cell Disease	NCT01322269 Phase 2	HQK-1001	Complete	HemaQuest
Effects of HQK-1001 in Patients With Sickle Cell Disease	NCT01601340 Phase 2	HQK-1001	Terminated	HemaQuest
Study to Determine the Maximum Tolerated Dose, Safety and Effectiveness of Pomalidomide for Patients With Sickle Cell Disease	NCT01522547 Phase 1	Pomalidomide	Complete	Celgene
Hemoglobin-modifying and anti-sickling agents				
Dose-Escalation Study of SCD-101 in Sickle Cell Disease	NCT02380079 Phase 1	SCD-101	Ongoing	Invenux; SUNY-Downstate Med Ctr
Safety Study of MP4CO in Adult Sickle Cell Patients	NCT01356485 Phase 1	MP4CO	Complete	Sangart
Study of SANGUINATE™ Versus Hydroxyurea in Sickle Cell Disease (SCD) Patients	NCT01848925 Phase 1	Sanguinate	Complete	Prolong Pharmaceuticals
Study of SANGUINATE™ In the Treatment of Sickle Cell Disease Patients With Vaso-Occlusive Crisis	NCT02411708 Phase 2	Sanguinate	Ongoing	Prolong Pharmaceuticals
A Study of the Efficacy and Safety of ICA-17043 (With or Without Hydroxyurea) in Patients With Sickle Cell Anemia.	NCT00040677 Phase 2	Senicapoc (ICA-17043)	Complete	Icagen
A Stratified Sickle Event Randomized Trial (ASSERT)	NCT00102791 Phase 3	Senicapoc (ICA-17043)	Terminated (lack of efficacy)	Icagen
A Study Evaluating the Long-Term Safety of ICA-17043 in Sickle Cell Disease Patients With or Without Hydroxyurea Therapy	NCT00294541 Phase 3	Senicapoc (ICA-17043)	Terminated	Icagen
A Single Dose Study of the Safety, Blood Levels and Biological Effects of Aes-103 Compared with Placebo in Subjects With Stable Sickle Cell Disease	NCT01597401 Phase 1	Aes-103	Complete	Baxalta US
Evaluation of Different Dose Regimens of Aes-103 Given for 28 Days to Subjects With Stable Sickle Cell Disease	NCT01987908 Phase 2	Aes-103	Terminated	Baxalta US

Table 4. Recently completed and ongoing studies involving anticoagulants

Study title	Clinical trials #/Phase	Intervention	Status	Primary sponsor
An Exploratory Study of Anticoagulation For Pulmonary Hypertension in Sickle Cell Disease	NCT01036802 Phase 2	Warfarin	Terminated	Univ. of North Carolina-Chapel Hill
Treatment of Sickle Cell Patients Hospitalized in Pain Crisis With Prophylactic Dose Low-molecular-weight Heparin (LMWH) Versus Placebo	NCT01419977 Phase 2	Dalteparin	Completed	Duke Univ.
Unfractionated Heparin in Acute Chest Syndrome: A Pilot Feasibility Randomized Controlled Trial of Unfractionated Heparin vs Standard of Care in Acute Chest Syndrome	NCT02098993 Phase 2	Unfractionated heparin	Recruiting	Univ. of Pittsburgh
The Effect of Factor Xa Inhibition, With Rivaroxaban, on the Pathology of Sickle Cell Disease	NCT02072668 Phase 2	Rivaroxiban	Recruiting	Univ. of North Carolina-Chapel Hill
Impact of Daily Prophylaxis Dose Anticoagulation With a Factor Xa Inhibitor (Apixaban) in Patients With Sickle Cell Disease	NCT02179177 Phase 2	Apixiban	Recruiting	Duke Univ.
A Pilot Study of *N*-acetylcysteine in Patients With Sickle Cell Disease	NCT01800526 Phase 0	N-acetyl cysteine	Recruiting	Puget Sound Blood Center

Conclusioni

Possibili prospettive terapeutiche nelle Emoglobinopatie:

terapie combinate-politerapie