Où en est-on de la thérapie génique ?

Journée filière MCGRE

31/01/2025

Laure Joseph et Isabelle Thuret

Dimitrievieska et al, Blood reviews 2024

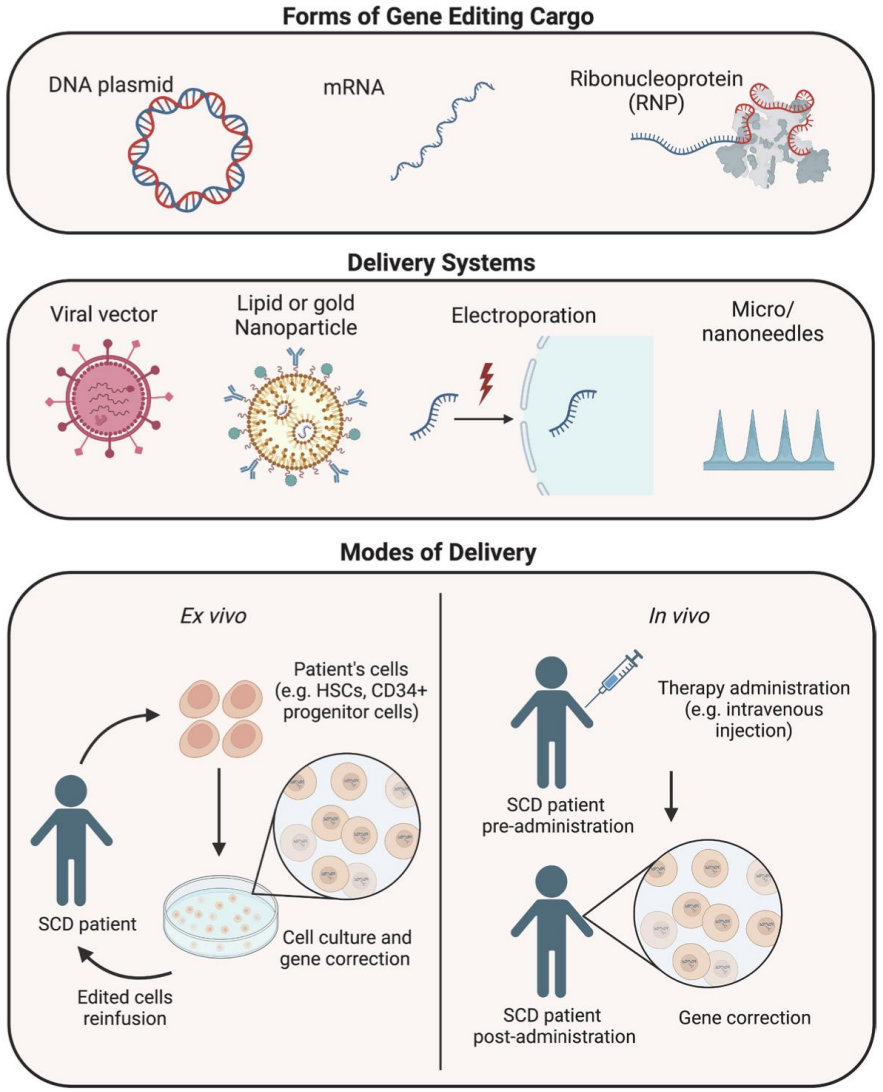
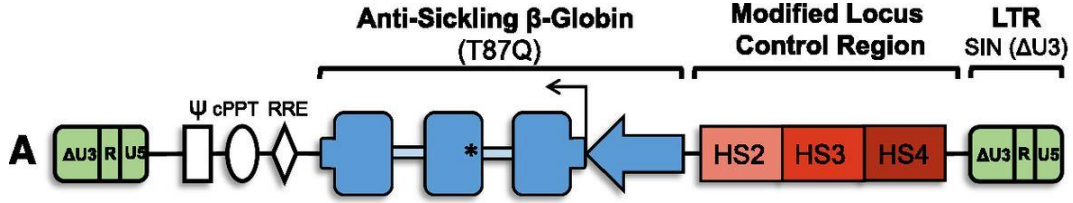


Fig. 3. Gene Editing: delivery methods. Schematic showing different aspects of gene editing delivery method that can be combined to design a gene editing strategy for sickle cell disease. **a)** Forms of gene editing components. Different forms in which targeted nucleases can be delivered . **b)** Delivery Systems. Different ways to deliver targeted nucleases, guide RNAs (sgRNA, gRNA, pegRNA) and donor templates. **c)** Modes of delivery. *Ex vivo* and *in vivo* strategies.

Thérapie génique

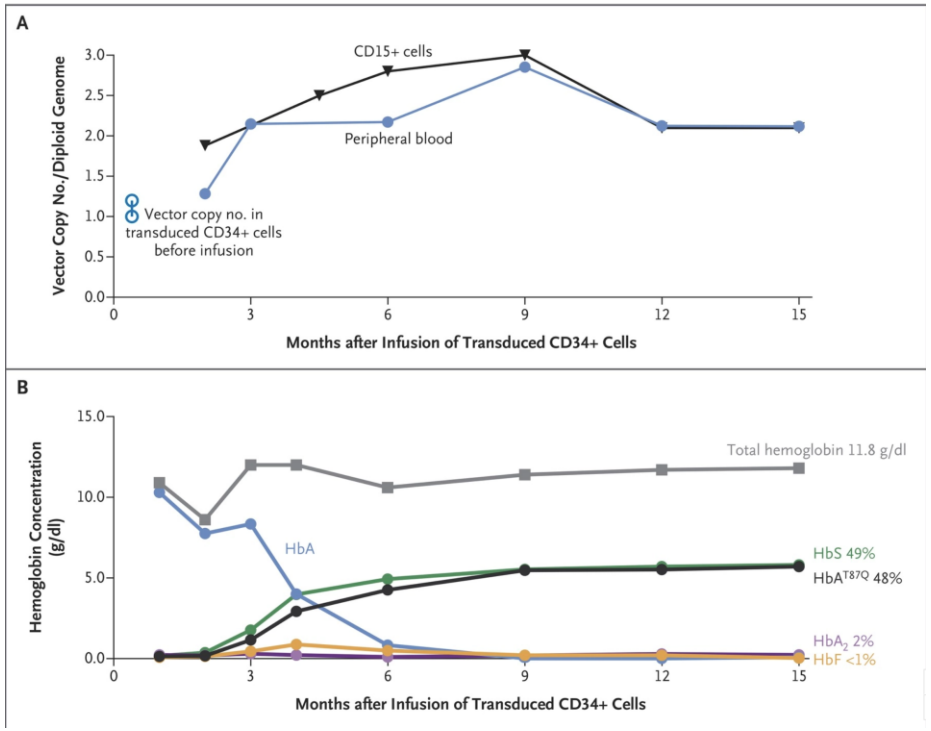
- Aujourd'hui :
  - Autogreffe de cellules souches hématopoïétiques (enrichies en fraction CD34+) génétiquement modifiées après un conditionnement myéloablatif.
  - Indication : patients atteints de SDM sévère (échec ou efficacité insuffisante HU) qui n'ont pas de donneur géno-identique et pas de vasculopathie cérébrale.
- 3 techniques
  - Addition de gènes
  - Edition de gènes (induction HbF)
  - Correction de gène

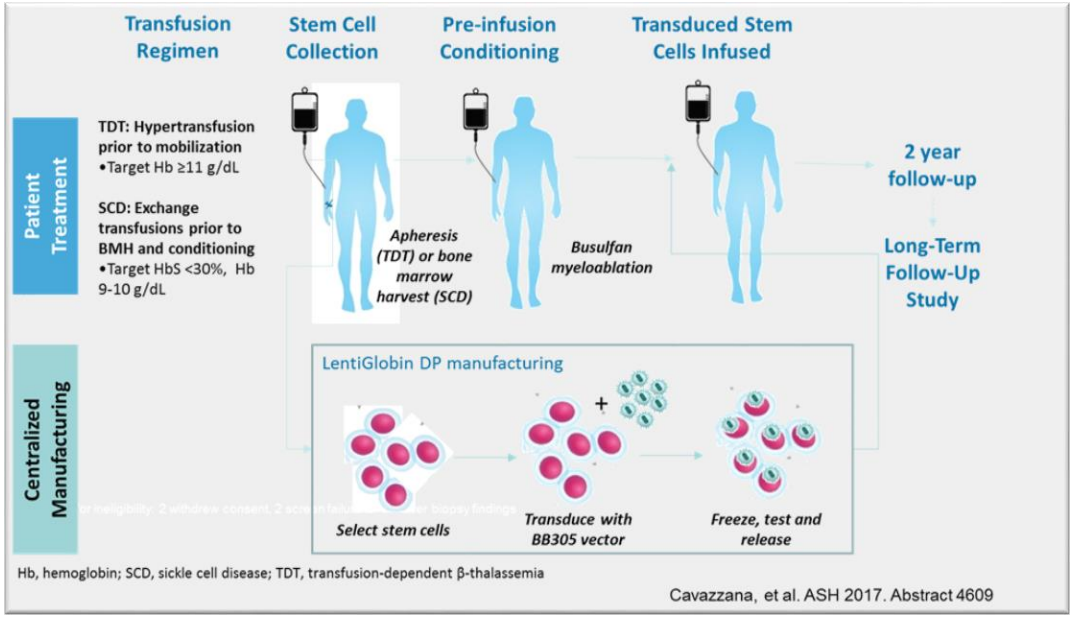
Addition de gènes



- HGB 205
- 3 patients drépanocytaires à Necker
  - Premier succès publié en 2017

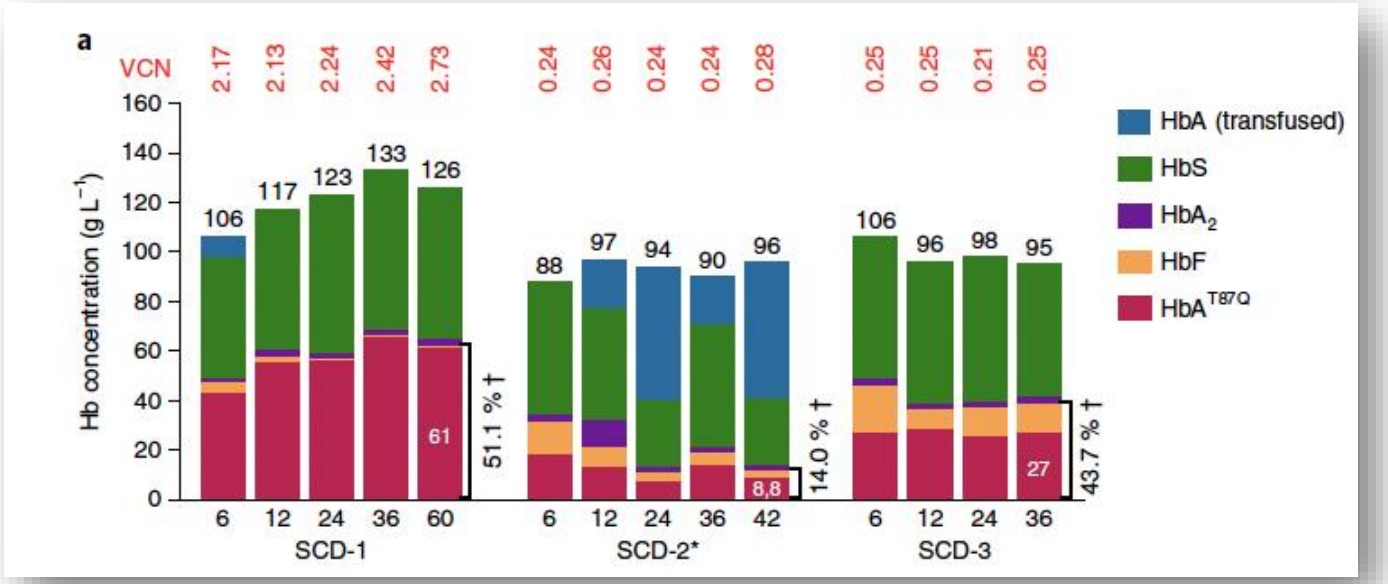
Megan D. Hoban et al. Blood 2016;127:839-848

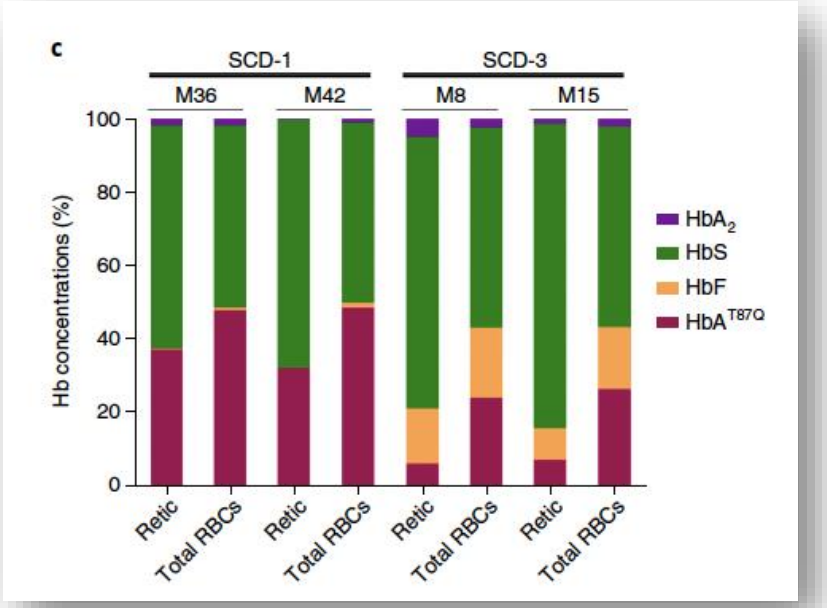




Ribeil et al, NEJM 2017

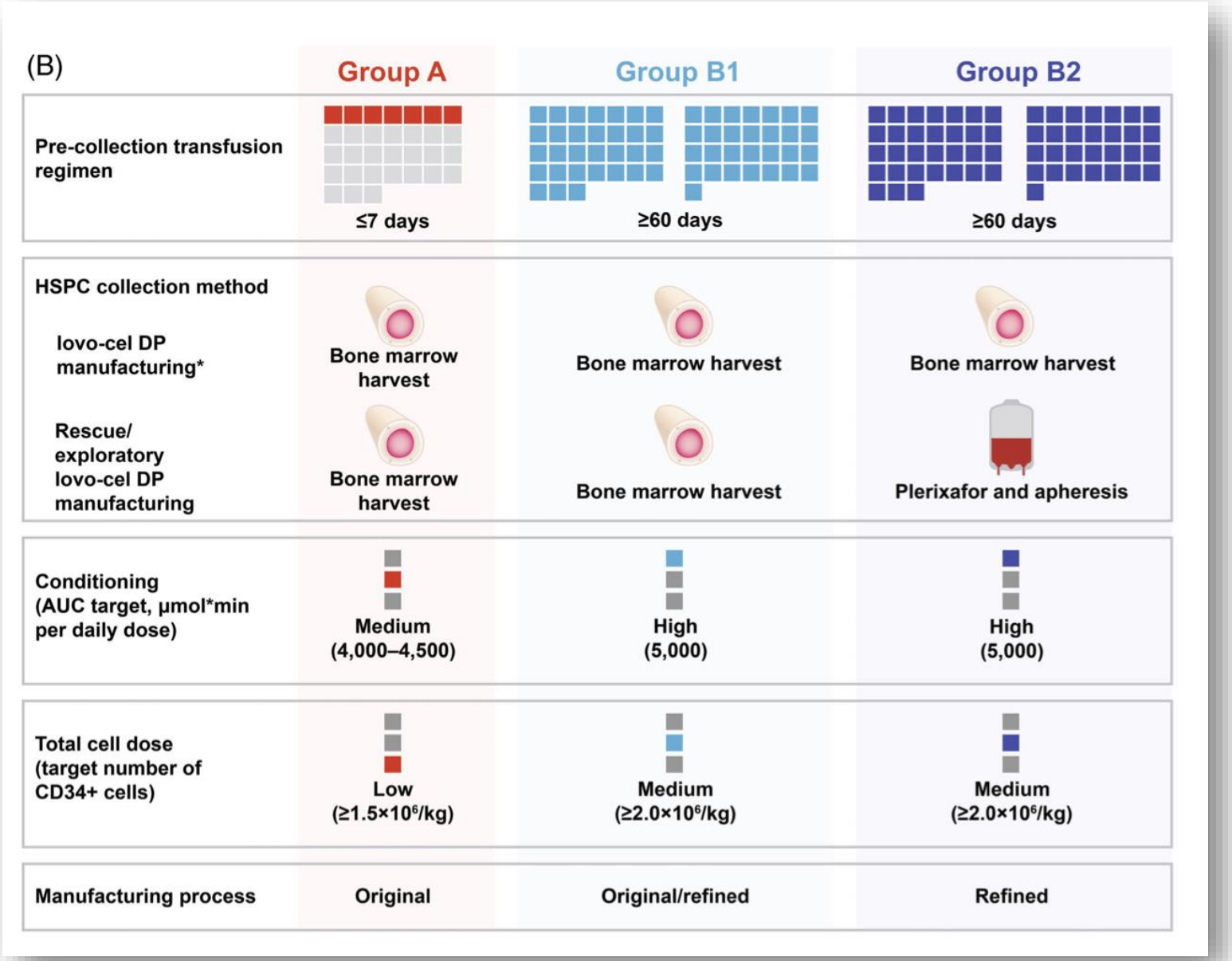
HGB 205 (suivi à long terme)





Magrin et al, Nature Medicine 2022

Protocole clinique HGB 205



(B)

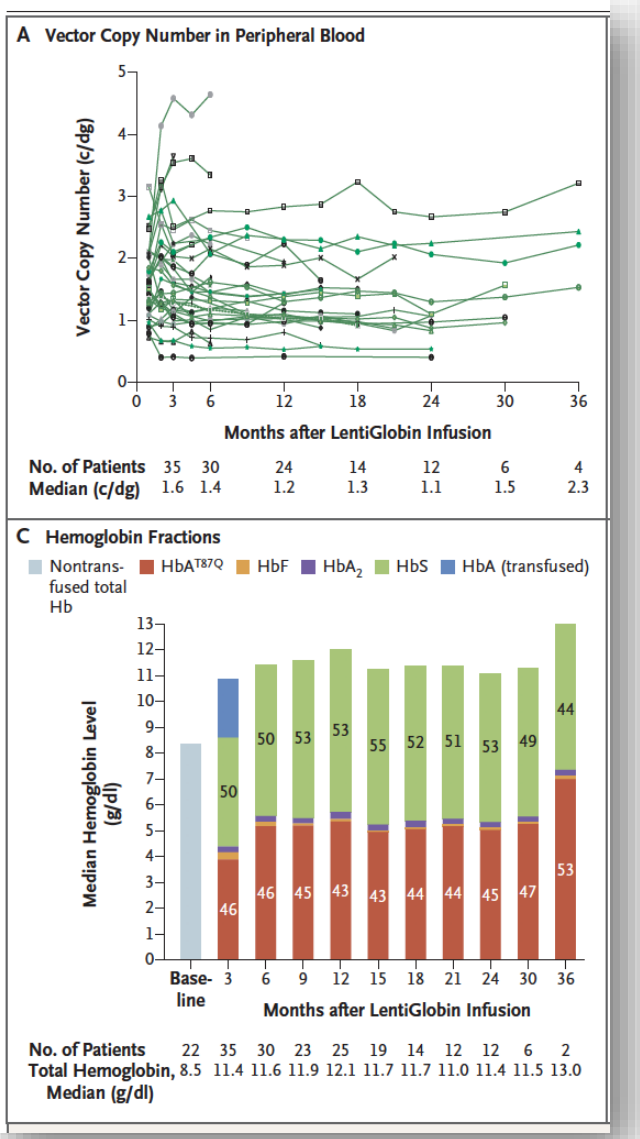
	Group A	Group B1	Group B2
Pre-collection transfusion regimen	≤7 days	≥60 days	≥60 days
HSPC collection method			
Iovo-cel DP manufacturing*	Bone marrow harvest	Bone marrow harvest	Bone marrow harvest
Rescue/ exploratory Iovo-cel DP manufacturing	Bone marrow harvest	Bone marrow harvest	Plerixafor and apheresis
Conditioning (AUC target, µmol*min per daily dose)	Medium (4,000–4,500)	High (5,000)	High (5,000)
Total cell dose (target number of CD34+ cells)	Low (≥1.5×10⁶/kg)	Medium (≥2.0×10⁶/kg)	Medium (≥2.0×10⁶/kg)
Manufacturing process	Original	Original/refined	Refined

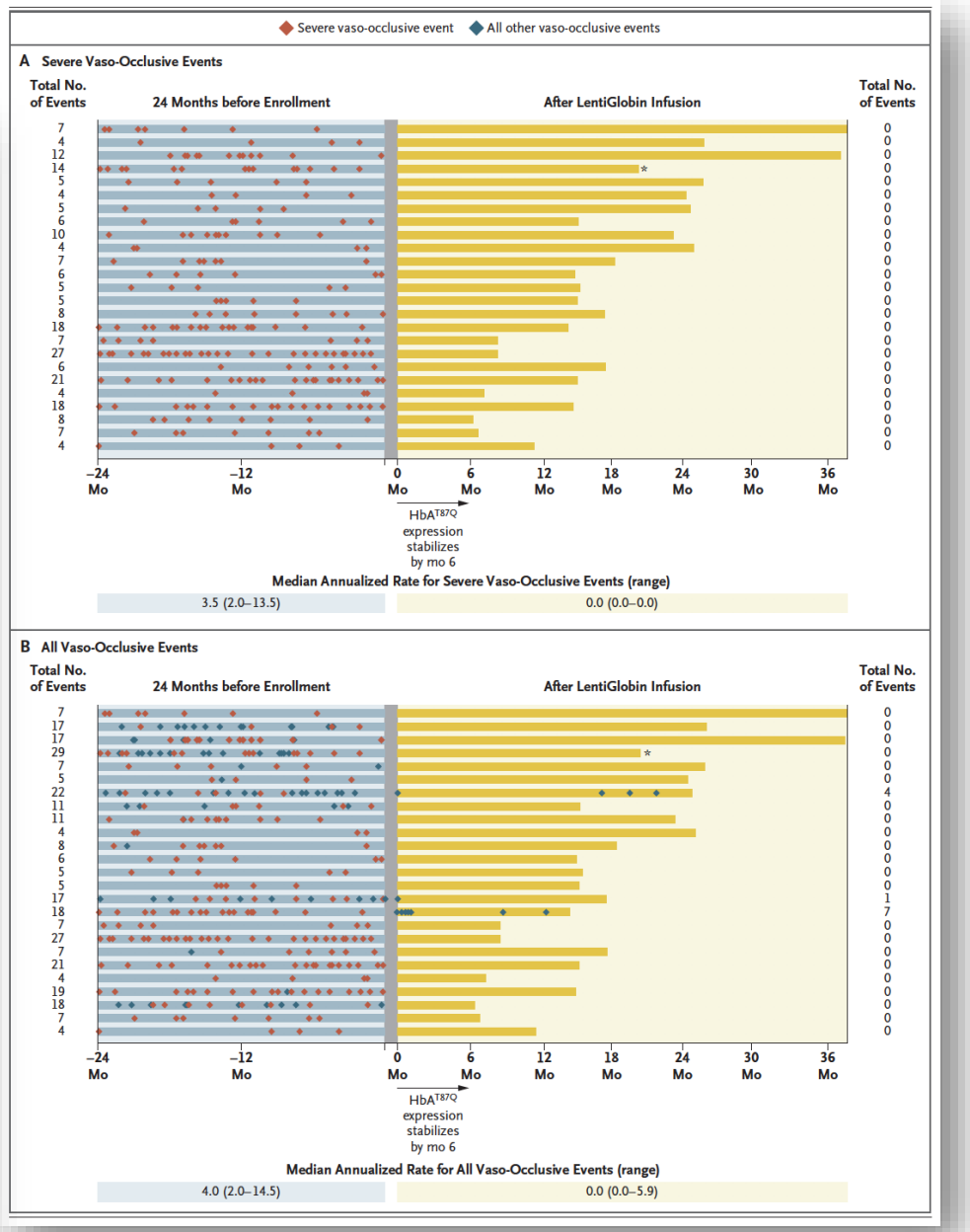
Julie Kanter et al, American journal of haematol. 2023

Protocole clinique HGB 206

- Group C
  - n=35
  - Médiane Hb 8,5 → 11g/dl
  - HbAT87Q >40% hb
  - Répartition hb T87Q = 85±8% RBC
  - Pas de recurrence de VOE sévère (n=25)

- Phase 3 HGB 210 : US

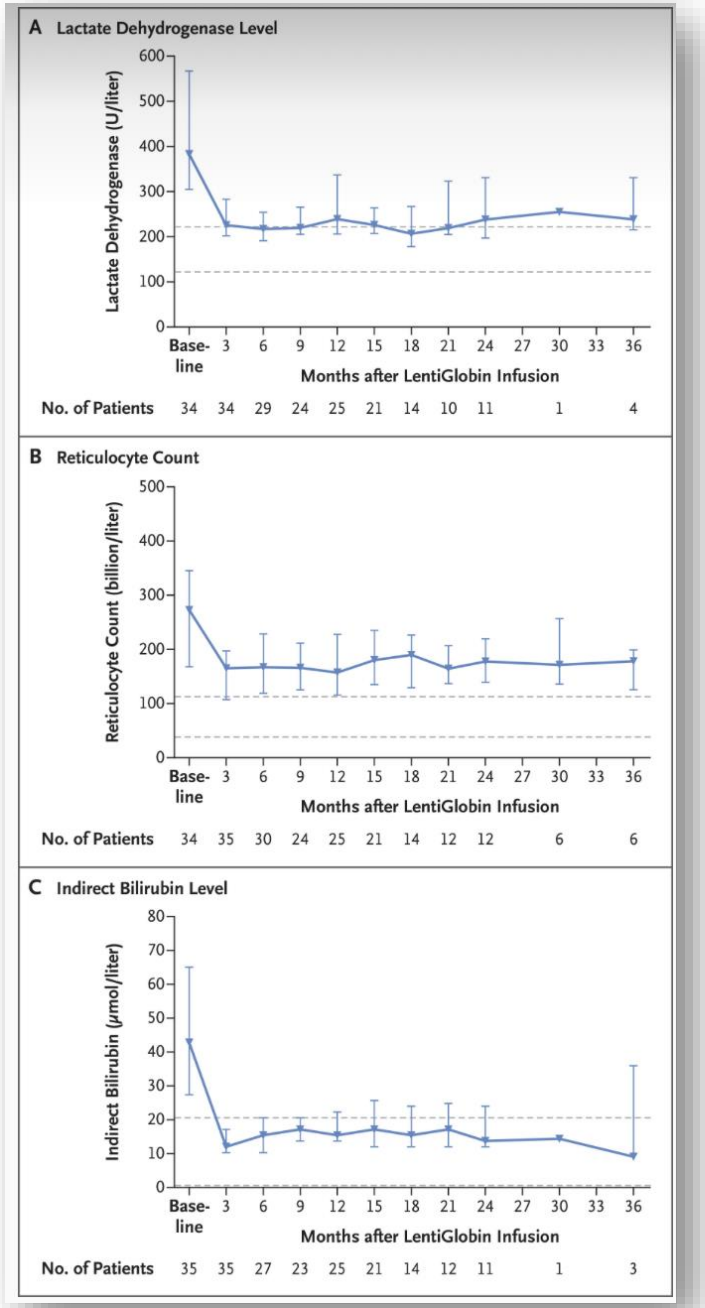




Julie Kanter et al, NEJM. 2021

Protocole clinique HGB 206

Nette amélioration des paramètres d'hémolyse avec normalisation de la biliribine libre mais réticulocytes toujours >120G/L et LDH subnormale ou légèrement élevée.



Drepaglobe essai français 2018

- Vecteur qui produit Hb thérapeutique βAS3
  - 3 mutations (G16D, E22A, T87Q) par rapport à la Béta globine → effet anti-falciformation
  - A22 et Q87 altèrent respectivement les contacts axiaux et latéraux nécessaires à la formation des polymères HbS. D16 augmente l'affinité pour les chaînes alpha, conférant ainsi à la βAS3 un avantage compétitif pour l'incorporation dans les tétramères d'Hb.

- n=4 patients traités
  - 2 patients ayant VCN <2 avec HbS entre 20-30% permettant l'arrêt des programmes d'échanges transfusionnels mais reprise de l'HU pour patient à 20% hbT. Persistance de l'anémie hémolytique chronique mais gain de >2g/dl d'hémoglobine totale pour les 2.
  - Puis 2 échecs consécutifs de la prise de greffe
    - Arrêt des inclusions

Post-Transcriptional Genetic Silencing of *BCL11A* to Treat Sickle Cell Disease

- Lentivirus
- **Efficacité intermédiaire**

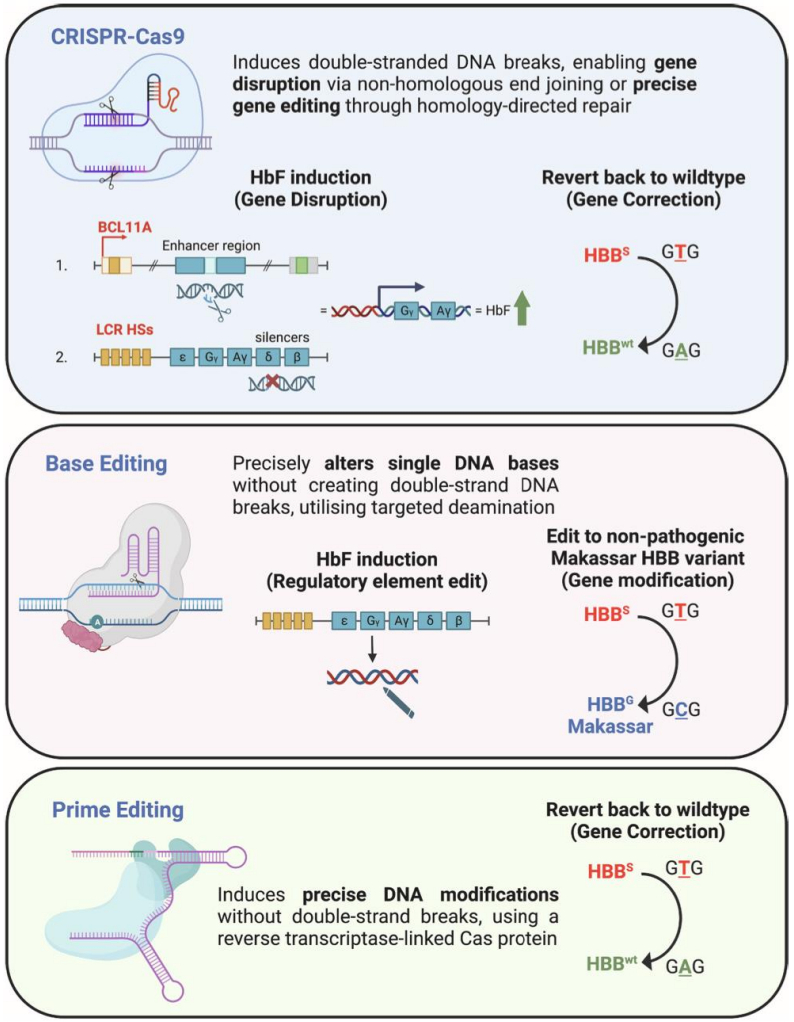
- Reactivation of HbF production via a short hairpin RNA (shRNA) targeting BCL11A mRNA embedded in a microRNA (shmiR)

Patient Number	Age in Yr, Sex	Genotype	Severe Symptoms	Receiving Transfusion, Hydroxyurea	CD34+ Cell Dose	VCN of Product	CD34+ Cells Transduced	Follow-up
					cells per kg	*copies per diploid genome*	*%*	*mo*
2	20, M	β^S/β^S	Previous stroke	Yes, No	5.1	3.3	95.8	29
3	25, M	β^S/β^S	Previous stroke	Yes, No	6.7	5.0	98.6	19
4	24, M	β^S/β^S	Priapism	No, Yes	5.2	3.3	95.5	20
6	16, F	β^S/β^0	Vaso-occlusive event, ACS	No, Yes	8.3	6.9	100.0	16
7	12, F	β^S/β^S	Previous stroke	Yes, No	6.1	2.8	93.1	12
8	7, M	β^S/β^S	Vaso-occlusive event	No, Yes	4.9	1.8	62.0	7

Patient Number	Months since Infusion	Hb	Hct	MCV	MCHC	HbF[‡]	F-Cells[§]
		g/dl	*%*	*fl*	*g/dl*	*%*	*%*
2	24	11.4	32.5	87.8	35.1	22.7	71.0
3[†]	18	9.5	28.9	86.3	32.9	20.4	58.9
4	21	11.1	31.2	84.8	35.6	31.9	81.9
6	15	11.0	32.5	76.0	33.8	38.8[‖]	65.3
7	12	11.0	31.4	81.1	35.0	29.0	70.6
8	6	9.3	25.5	88.9	36.5	41.3	93.6

Esrick et al, NEJM 2021

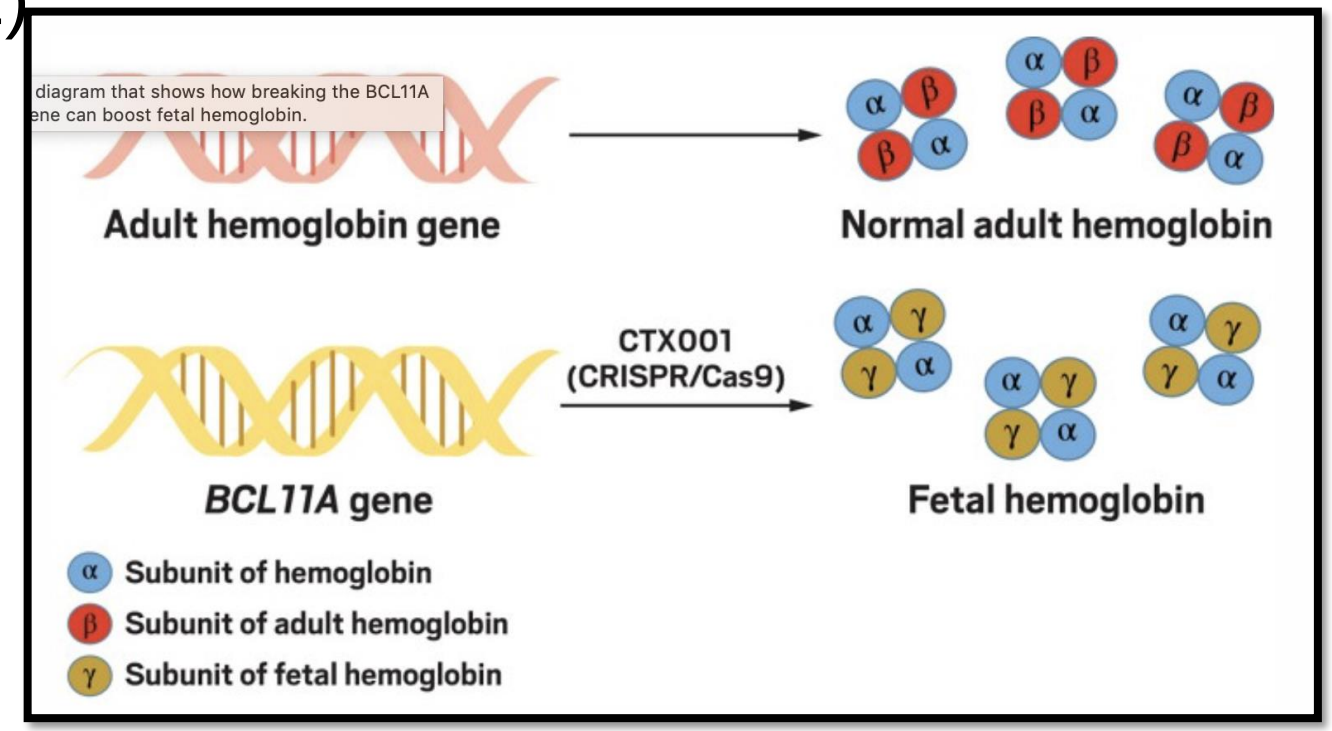
Dimitrievieska et al, Blood reviews 2024



Gene Editing technologies for SCD: CRISPR-Cas9, Base Editing, and Prime Editing a) CRISPR-Cas9 can be used to either correct the mutation to the wild
induce fetal haemoglobin (HbF) expression by inducing a change in the *BCL11A* erythroid-specific enhancer or deleting part of the HbF silencers which
ion is controlled by LCR hypersensitive sites . **b)** Adenine Base Editor can edit the regulatory elements controlling HbF expression or convert HBBS to a
ar non-pathogenic variant HBBG. **c)** Prime Editing can be used to correct the HBB mutation back to the wild type without the need for double-stranded breaks.

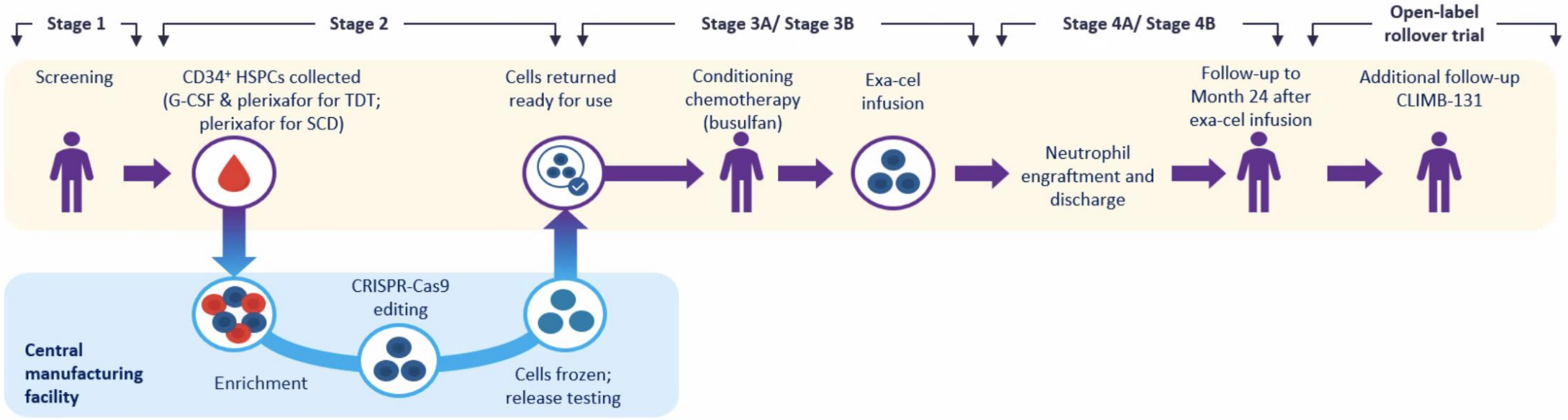
Edition de gènes : HbF Induction

- Gene expression modification to increase foetal haemoglobin production: a phase 1-2 trial using CrispR-Cas 9 technology (CTX001)



Frangoul et al, NEJM 2020

Pivotal Phase 3 Trials of Exa-cel in Participants With TDT and Severe SCD



	CLIMB THAL-111 in TDT	CLIMB SCD-121 in SCD
Study Design	International, multicenter, open-label, single-arm, 2-year Phase 3 trial of a single infusion of exa-cel (NCT03655678)	International, multicenter, open-label, single-arm, 2-year Phase 3 trial of a single infusion of exa-cel (NCT03745287)
Participants Dosed	48 participants dosed	35 participants dosed
Key Inclusion Criteria	Twelve to 35 years of age with TDT, including β^0/β^0 genotypes, defined as a history of ≥100 mL/kg/year or ≥10 units/year of pRBC transfusions in the previous 2 years	Twelve to 35 years of age with severe SCD and a history of ≥2 severe VOCs per year in the previous 2 years
Pre-specified Analysis	• Full Analysis Set: participants who received exa-cel infusion • Primary Efficacy Set: participants followed for ≥16 months after exa-cel infusion (evaluable for primary & key secondary endpoints) • Pre-specified interim analysis: conducted when primary efficacy set included 27 participants in CLIMB THAL-111 and 17 participants in CLIMB SCD-121	

Participants who complete CLIMB THAL-111 or CLIMB SCD-121 can enroll in CLIMB-131 for 13 years of additional follow-up

The data cutoff date for the pre-specified interim analysis was 06Sept2022 for CLIMB THAL-111 and 16Sept2022 for CLIMB SCD-121.

CRISPR-Cas9, clustered regularly interspaced short palindromic repeats-associated 9 nuclease; **exa-cel,** exagamglogene autotemcel; **G-CSF,** granulocyte colony-stimulating factor; **HSPC,** hematopoietic stem and progenitor cell; **pRBC,** packed red blood cell; **SCD,** sickle cell disease; **TDT,** transfusion dependent β-thalassemia; **VOC**, vaso-occlusive crisis.

Pivotal Trial Endpoints

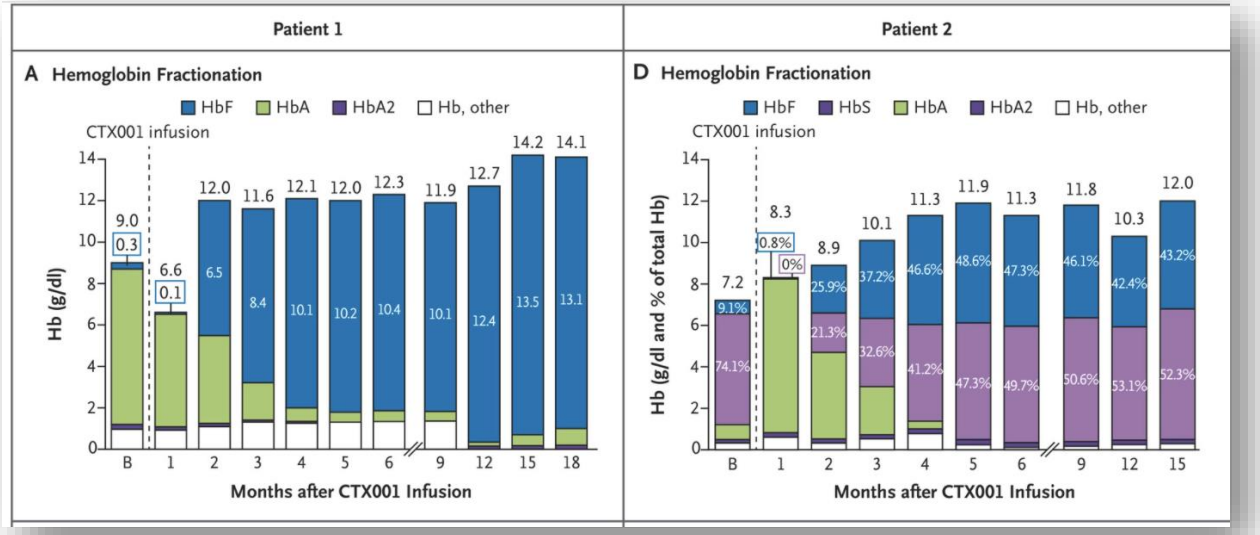
	TDT	SCD
Primary Efficacy Endpoint	Proportion of participants **transfusion independent for 12 consecutive months** while maintaining a weighted average hemoglobin ≥9 g/dL **(TI12)** ○ Assessed starting 60 days after last RBC transfusion for post-transplant support or TDT disease management	Proportion of participants **free of severe VOCs for ≥12 consecutive months (VF12)** ○ Assessed starting 60 days after last RBC transfusion for post-transplant support or SCD disease management
Key Secondary Efficacy Endpoint	Proportion of participants **transfusion independent for 6 consecutive months** while maintaining a weighted average hemoglobin ≥9 g/dL **(TI6)** ○ Assessed starting 60 days after last RBC transfusion for post-transplant support or TDT disease management	Proportion of participants **free from in-patient hospitalization for severe VOCs for ≥12 consecutive months (HF12)** ○ Assessed starting 60 days after last RBC transfusion for post-transplant support or SCD disease management
Secondary & Other Efficacy Endpoints*	• Total hemoglobin concentration • Fetal hemoglobin concentration • Proportion of F-cells • Proportion of alleles with intended genetic modification in peripheral blood • Proportion of alleles with intended genetic modification in CD34+ cells of the bone marrow • Change over time in patient reported outcome measures	
Safety Endpoints	• Neutrophil and platelet engraftment • Safety and tolerability assessments, including adverse events, clinical laboratory values, and vital signs	

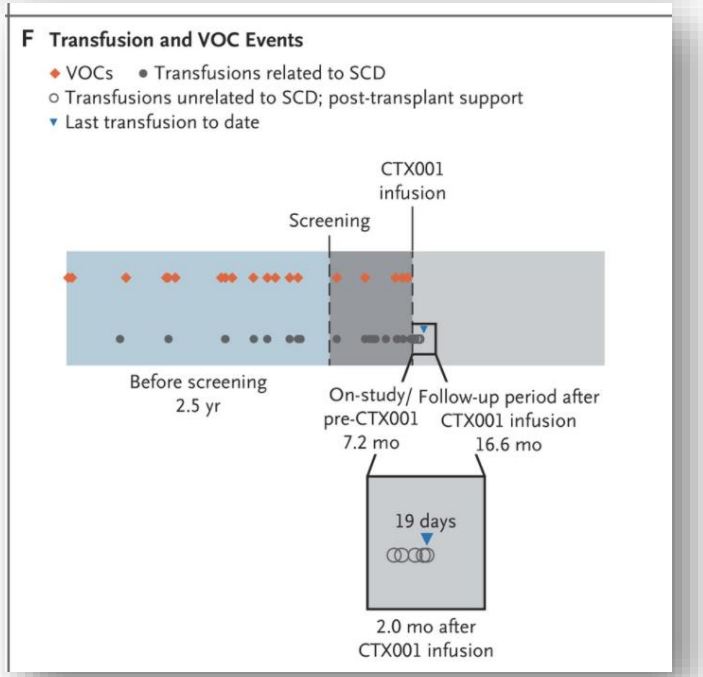
The clinical protocol for these trials included additional secondary endpoints.

-cells, circulating RBCs expressing detectable levels of HbF; **LDH,** lactate dehydrogenase; **RBC,** red blood cell; **SCD,** sickle cell disease; **TDT,** transfusion dependent β-thalassemia; **VOC**, vaso-occlusive crisis.

Induction HbF

- Allelic correction rate >80%
- EHA June 2021
  - n=15 TDT including 6 β0/β0 or severe genotypes all independent of transfusion after infusion
  - n=7 SCD: no recurrence of CVO 7 patients with follow-up >1 year: durable response Target 90 patients (45 TDT, 45 SCD)



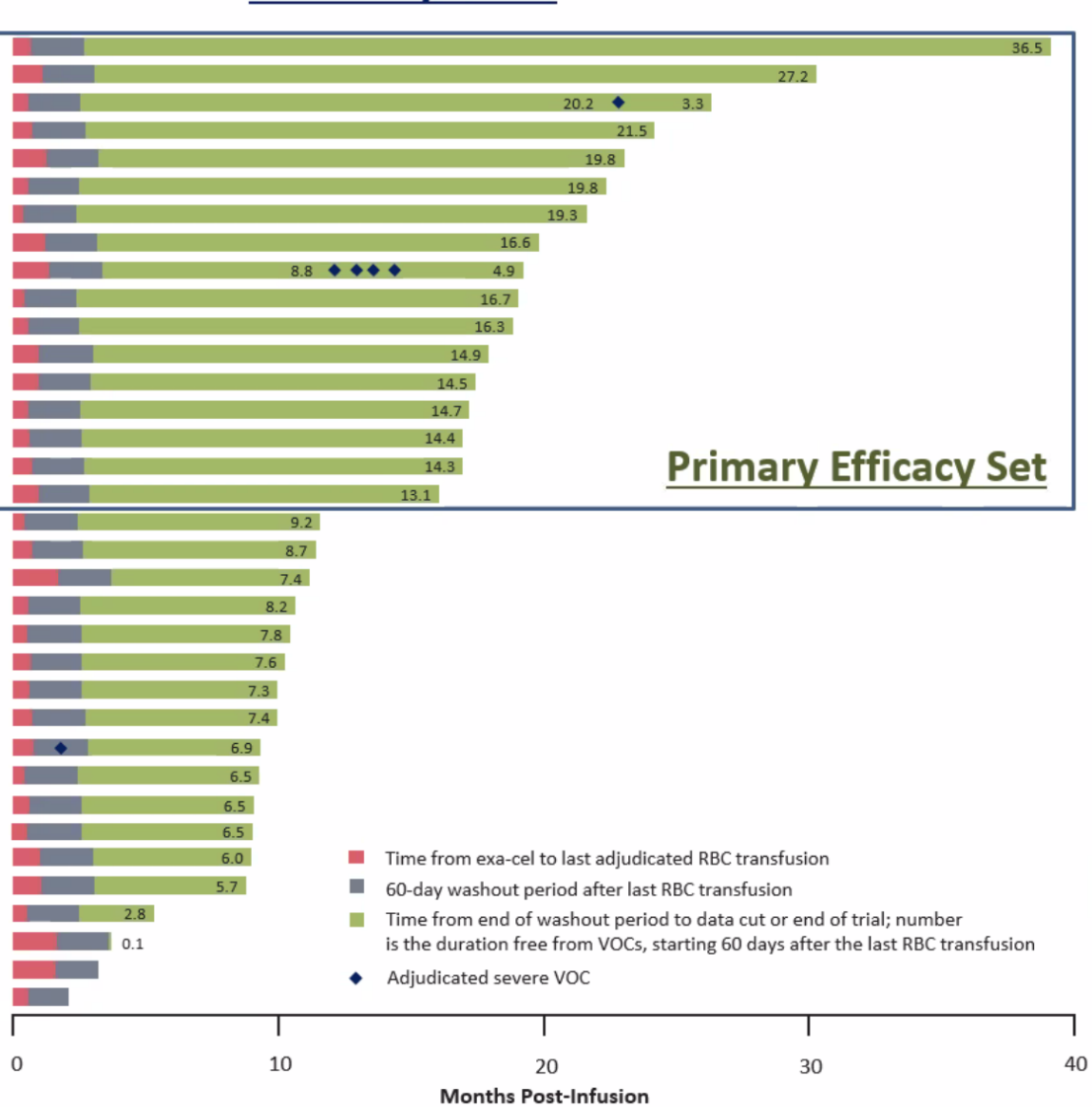


Frangoul et al, NEJM 2020

SCD: Participants Who Achieved Freedom from VOC (VF12) Maintained VOC-Free From 13.1 Months to 36.5 Months

Full Analysis Set

Participant #	Total Follow-up	Historical Severe VOCs[c]
1[a]	39.1	7
2[a]	30.3	8.5
3[a]	26.3	4
4[a]	24.2	2.5
5[a]	23.0	5.5
6[a]	22.3	9.5
7[a]	21.6	4
8[a]	19.8	6
9[a]	19.3	3
10[a]	19.1	2
11[a]	18.8	2.5
12[a]	17.9	2.5
13[a]	17.4	4.5
14[a]	17.2	8.5
15[a]	17.0	4
16[a]	17.0	2.5
17[a]	16.0	2
18	11.6	2.5
19	11.4	2
20	11.1	3
21	10.7	2
22	10.4	2.5
23	10.2	5.5
24	10.0	2
25	10.0	2
26	9.3	4
27	9.3	2.5
28	9.0	3.5
29	9.0	4
30[b]	8.9	3
31	8.8	3.5
32	5.3	18.5
33	3.7	4
34	3.2	2
35	2.0	3.5



- **For participants achieving VF12, duration of VOC-free was** 13.1 to 36.5 months **(mean 18.7 months)**
  - Participants **stopped transfusions** after a mean of 22.5 days
- **One participant** did not achieve VF12 but **achieved HF12**
  - Participant had multiple **complex comorbidities**, including a history of chronic pain
- **15 of 16 participants** remained **VOC-free through follow-up**
  - **One participant** had a **VOC** in the setting of a parvovirus **infection** 22.8 months after exa-cel infusion
  - Participant **fully recovered** and has been **VOC-free since**

Each row in the figure represents an individual participants. All VOCs were adjudicated by the Independent Adjudication Committee.
[a]Participants evaluable for the primary endpoint; [b]Death from respiratory failure due to COVID-19 infection; [c]Pre-trial severe VOCs annualized over 2 years.

Demographics and Baseline Clinical Characteristics[1]

	Full Analysis Set[a] N = 46	Primary Efficacy Set[b] N = 39
Age at screening, years, mean (SD)	21.4 (6.0)	21.2 (6.0)
≥12 and <18 years, n (%)	12 (26.1)	11 (28.2)
≥18 and ≤35 years, n (%)	34 (73.9)	28 (71.8)
Sex, n (%)		
Male	25 (54.3)	23 (59.0)
Female	21 (45.7)	16 (41.0)
Genotype, n (%)		
β^s/β^s	41 (89.1)	36 (92.3)
β^s/β^0	2 (6.5)	2 (5.1)
β^s/β^+	2 (4.3)	1 (2.6)
α-globin gene deletion status, n (%)		
One-gene deletion	16 (34.8)	12 (30.8)
Two-gene deletions	2 (4.3)	2 (5.1)
Historical VOC episodes per year,[c] mean (range)	4.2 (2.0, 18.5)	4.1 (2.0, 18.5)
Historical in-patient hospitalisations for severe VOCs per year,[a] mean (range)	2.7 (0.0, 9.5)	2.6 (0.5, 8.5)

[a] Full Analysis Set includes participants who received exa-cel infusion.
[b] Primary Efficacy Set includes participants who were followed for ≥16 months after exa-cel infusion (evaluable for primary & key secondary endpoints).
[c] Annualised over 2 years before screening.

EHA 2024, Abstract S273 "Exagamglogene Autotemcel For Severe Sickle Cell Disease,"

Treatment and Engraftment Results[1]

	Full Analysis Set[a] N = 46
Number of mobilisation cycles, median (range)	2.0 (1.00, 6.00)
Exa-cel dose: 10^6 x $CD34^+$ cells/kg, mean (range)	4.7 (2.9, 14.4)
Duration (months) of follow-up after exa-cel infusion[b], mean (range)	28.2 (8.2, 57.4)
Neutrophil Engraftment[c]	
Time to neutrophil engraftment (days), median (range)	27.0 (15, 40)
Duration of neutropenia (absolute neutrophil count <500 cells/uL) (days), median (range)	17.0 (6, 30)
Platelet Engraftment[d]	
Time to platelet engraftment (days), median (range)	34.5 (23, 126)
Time to last RBC transfusion (days), median (range)	19.5 (11, 91)
Time to hospital discharge[e] (days), median (range)	31.5 (21, 54)

[a] Full Analysis Set includes participants who received exa-cel infusion.
[b] Duration of follow-up include both CLIMB SCD-121 and CLIMB-131 trials.
[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 ≥50,000/μL on 3 different days.
[e] Defined as the number of days from exa-cel infusion to hospital discharge.

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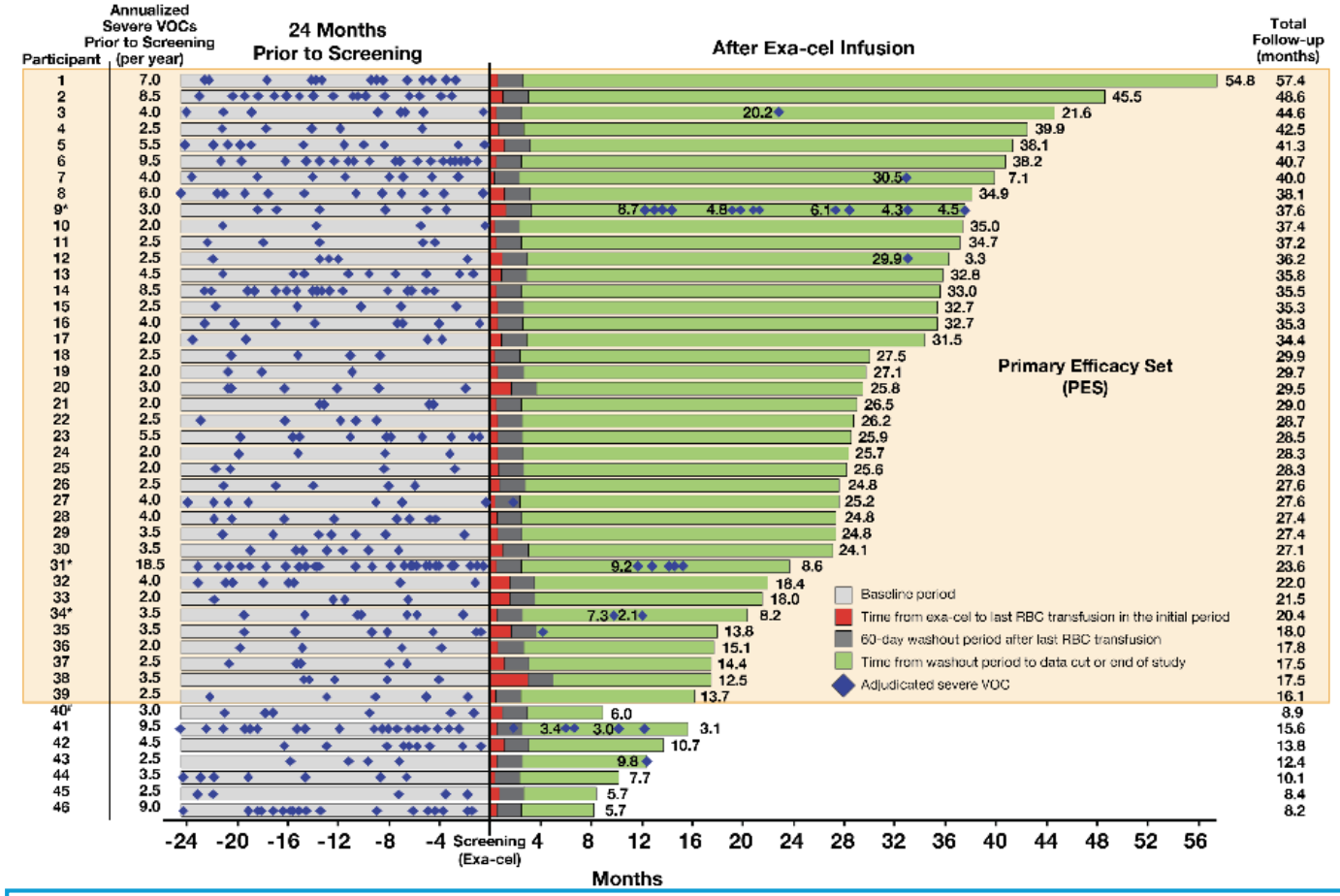
Severe VOC Status After Exa-cel Infusion[1]



- 36 of 39 evaluable participants (92.3%) achieved VF12 with mean duration of VOC-free period 27.9 months (range 12.5 to 54.8) (PES)

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

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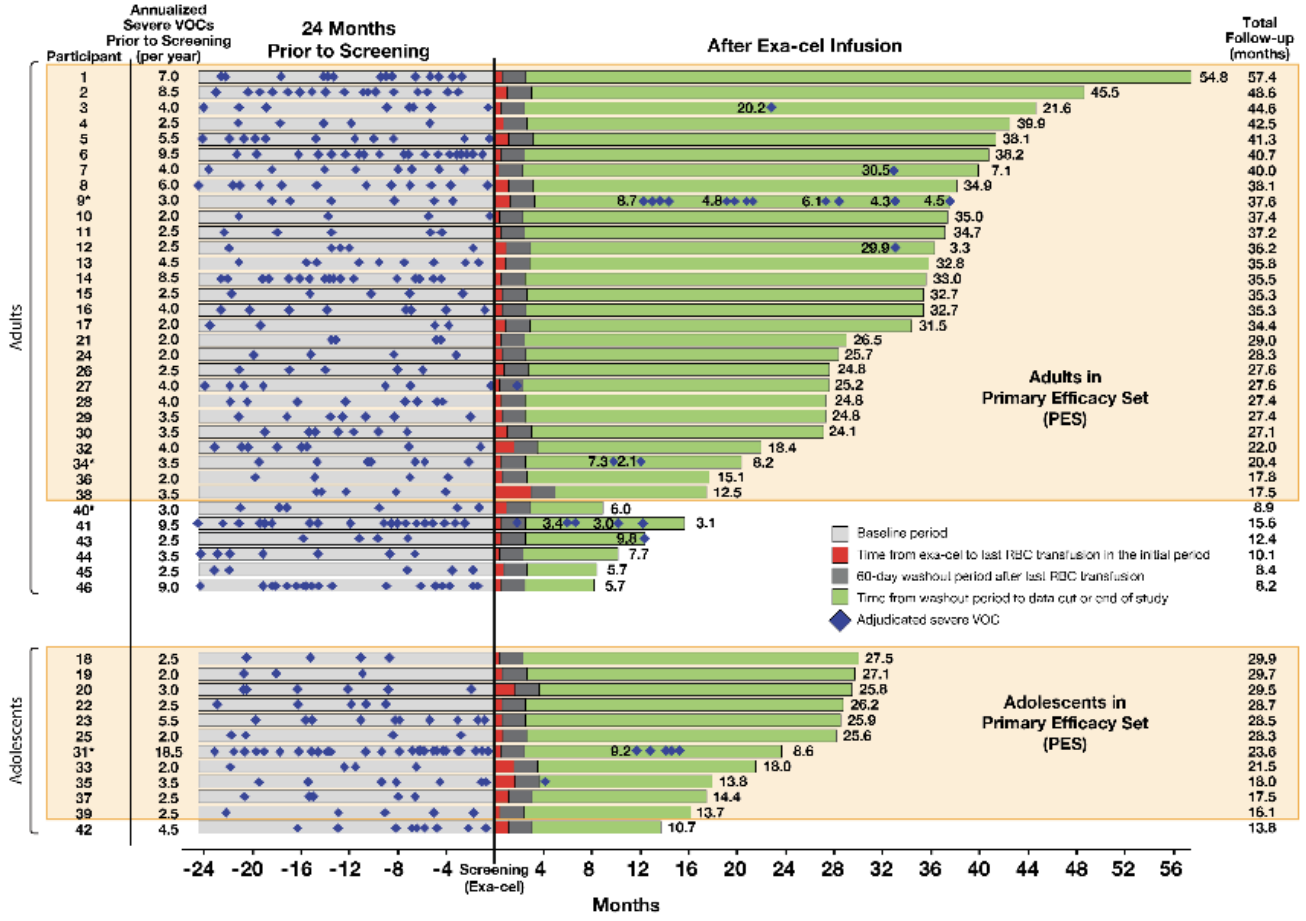
Severe VOC Status After Exa-cel Infusion Across Age Groups[1]



- 26 of 28 evaluable adults (92.9%) achieved VF12
- 10 of 11 evaluable adolescents (90.9%) achieved VF12

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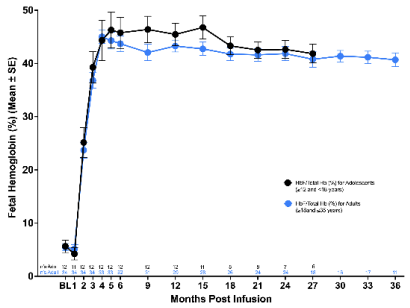
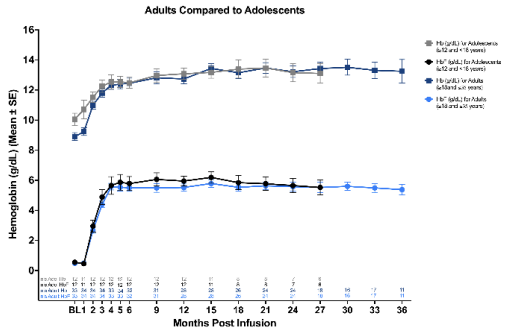
Total Haemoglobin and Foetal Haemoglobin Across Age Groups[1]

HbF Percentage



- **Mean (range) HbF percentage in adolescents:** 45.5 (37.7, 64.7) at month 12; 42.6 (37.6, 51.1) at month 24
- **Mean (range) HbF percentage in adults:** 43.3 (31.3, 59.1) at month 12; 41.8 (26.9, 53.0) at month 24

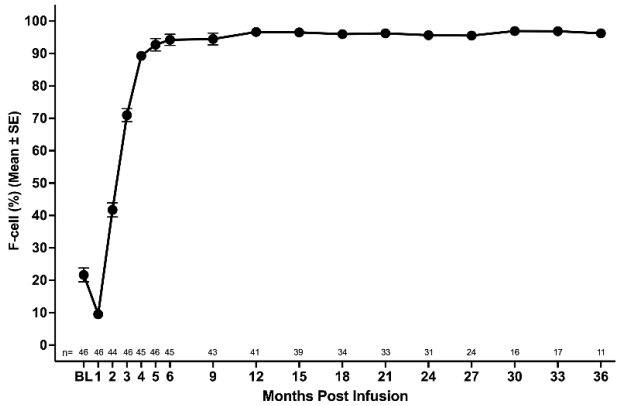
Total Hb and HbF



- **Mean (range) Hb (g/dL) in adolescents:** 13.1 (11.2, 15.7) at month 12; 13.2 (12.0, 16.5) at month 24
- **Mean (range) Hb (g/dL) in adults:** 12.7 (9.3, 15.7) at month 12; 13.2 (10.5, 17.3) at month 24

Pancellular Distribution Following Exa-cel Infusion[1]

F-Cells



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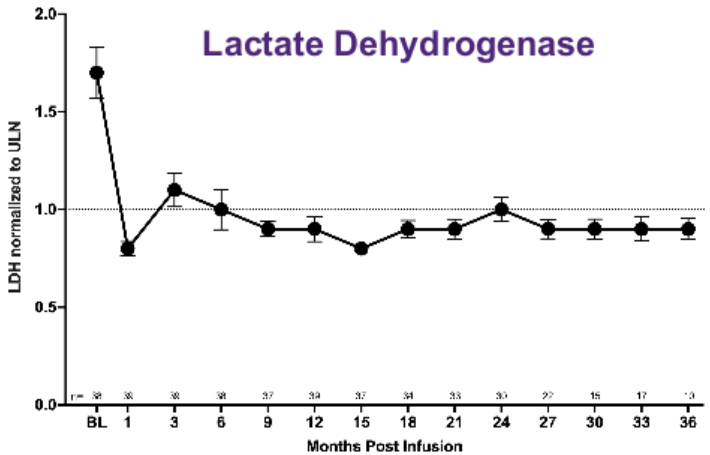
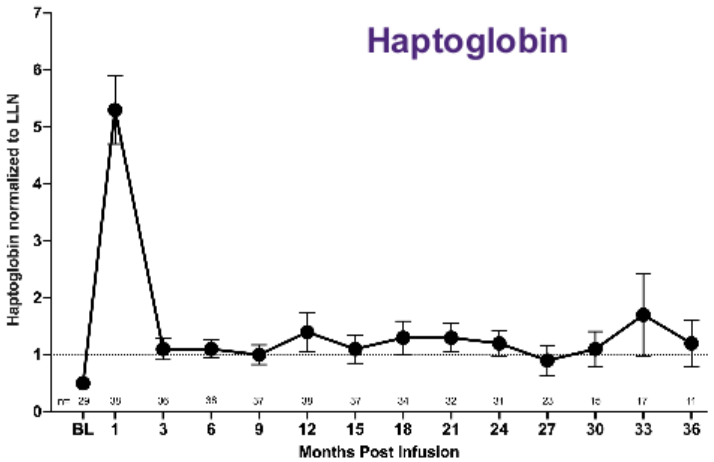
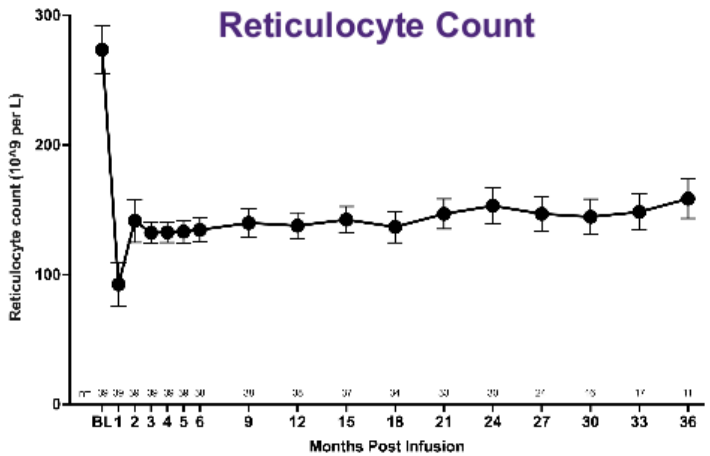
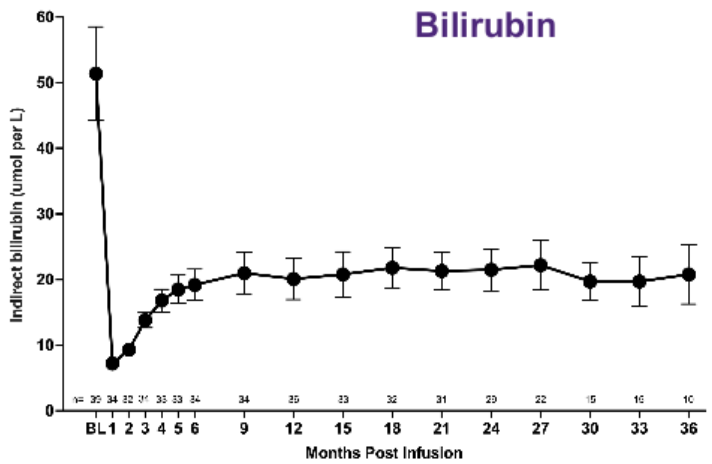
Markers of Haemolysis[1]









EHA 2024, Abstract S273 “Exagamglogene Autotemcel For Severe Sickle Cell Disease,”

Patient-Reported Outcome Measures in Adults[1]

Figure 3. Change from Baseline in FACT-G Total Score in Adults in Primary Efficacy Set

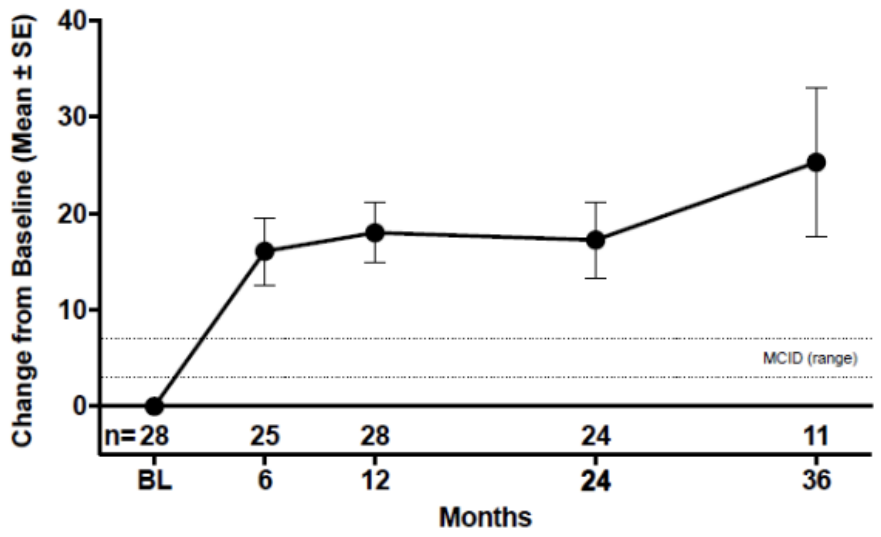
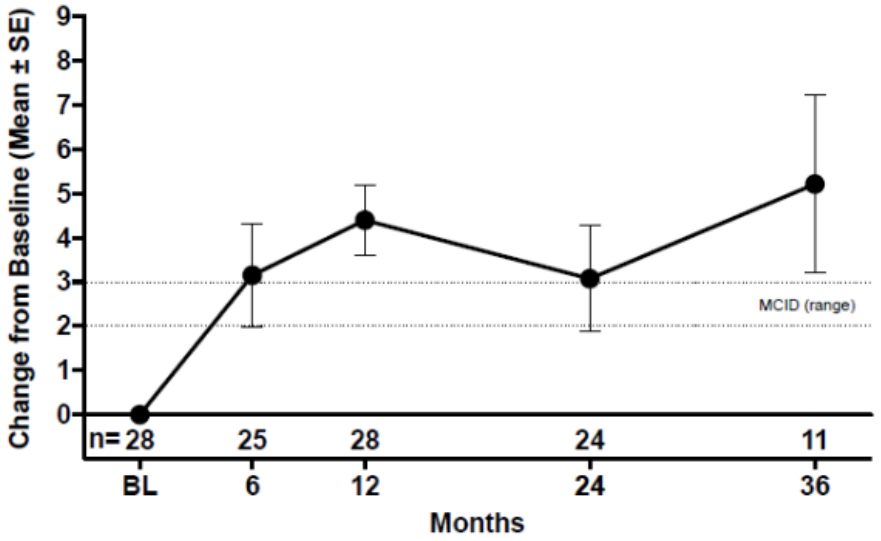


Figure 4. Change from Baseline in BMT Scores in Adults in Primary Efficacy Set



EHA 2024, Abstract S273 "Exagamglogene Autotemcel For Severe Sickle Cell Disease,"

Etude RUBY CRISPR/Cas12a

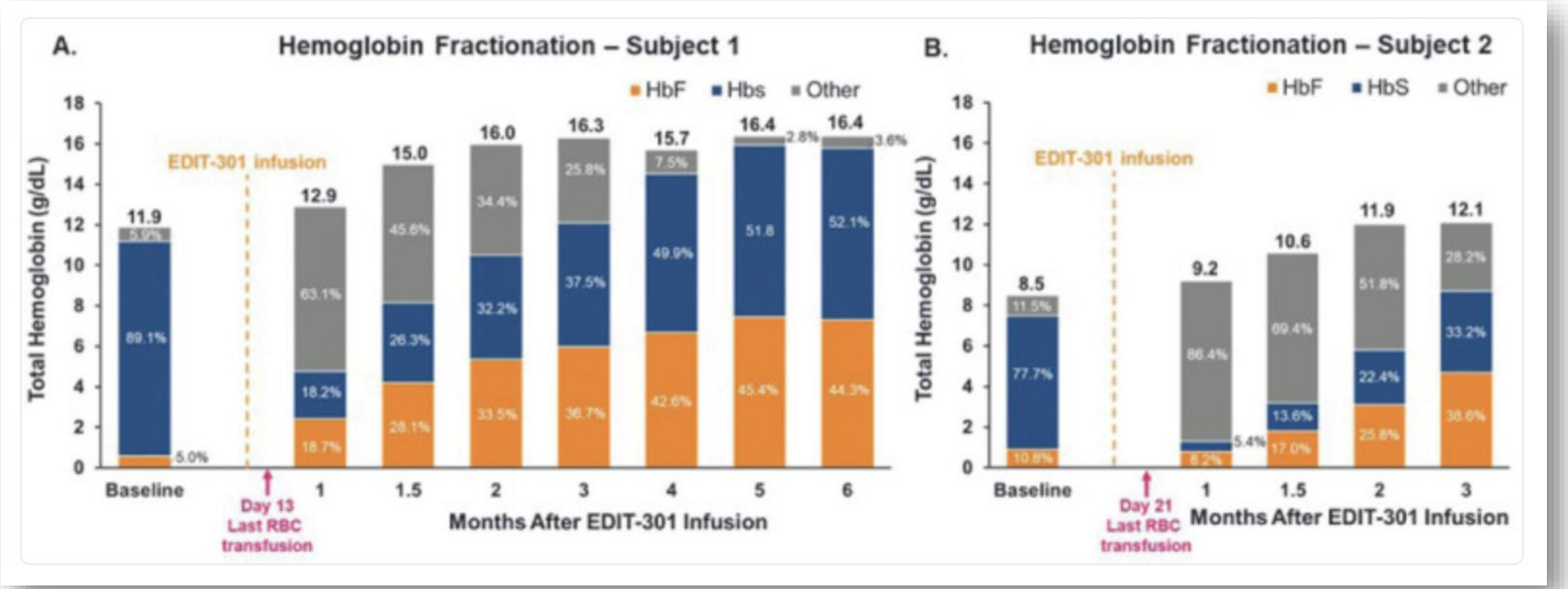
- Edition CD34+ au niveau de la boîte CCAAT distale (-118 à -113) des régions promotrices du gène de la γ-globine (HBG1/2) à l'aide d'une nucléase d'édition de gènes hautement spécifique et efficace, AsCas12a.

- Ces modifications imitent les variantes naturelles de la persistance héréditaire de l'HbF dans les promoteurs HBG1/2 et réactivent l'expression de la γ-globine, ce qui entraîne une production soutenue et cliniquement significative d'HbF (>80% in vitro).

- A Phase I/II, multicenter, open-label, single-arm study, evaluates the safety, tolerability, and efficacy of EDIT-301 in subjects with severe SCD. Severe SCD defined as ≥2 severe vaso-occlusive events (VOEs) per year in the 2-year period prior to informed consent

RUBY study CRISPR/Cas12a

- Four subjects have received EDIT-301 treatment. One cycle of apheresis sufficient for all patients
- HbF levels >35%, no reported VOEs.
- Hb increased by 4.5 g/dL from baseline (BL) to 16.4 g/dL at 6 months (Subject 1) and increased by 3.6 g/dL from BL to 12.1 g/dL at 3 months post-EDIT-301 infusion (Subject 2). Percentage of F-cells was 96.5% at 6 months (Subject 1).



R Hanna et al, abstract EHA 2024

ASH 2024

Reni-Cel, an Investigational AsCas12a Gene-Edited Cell Medicine, Led to Sustained Hemoglobin Normalization and Increased Fetal Hemoglobin in Patients with Severe Sickle Cell Disease Treated in the RUBY Trial

- October 29, 2024, n=28 , median of 9.5 months post-reni-cel infusion, with 11 patients having >1 year follow-up.
- Since reni-cel treatment, 27 of the 28 patients were free of vaso-occlusive events (VOEs).
- Mean total hemoglobin increasing from 9.8 g/dL at baseline to 13.8 g/dL at Month 6 (n=18)., fetal hemoglobin (HbF) ≥40% with a mean HbF percentage of 48.1% (n=18).
- The mean percentage of F-cells increased early and was sustained at >90% from month 4 through last follow-up (n=20).
- Markers of hemolysis, including absolute reticulocyte count, indirect bilirubin, lactate dehydrogenase, and haptoglobin, improved or normalized by Month 6 and were generally maintained or improved as of last follow-up.
- Sustained clinically meaningful improvements were observed in pain, physical, and social patient-reported outcome domains following treatment with reni-cel.
- Median time to neutrophil engraftment of 23 days and median time to platelet engraftment of 25 days, which is important for limiting infection and bleeding risk. Two serious adverse events (SAEs) assessed by the investigators as possibly related to reni-cel treatment have been reported in the RUBY trial.

BEACON **(ASH 2024)** ***Phase 1/2 Study Evaluating the Safety and Efficacy of a Single Dose of Autologous CD34+ Base Edited Hematopoietic Stem Cells (BEAM-101) in Patients with Sickle Cell Disease with Severe Vaso-Occlusive Crises***

- Edition de base ex-vivo : substitution de A vers G dans le promoteur du gène HBG1/2 qui code pour la gamma globine.
- Modification du site de fixation du répresseur de la synthèse d'HbF BCL11A permettant une réactivation de la production de celle-ci.
- Excellents résultats en terme d'HbF produite au-delà de 60% d'hémoglobine chez quatre patients ayant un recul suffisant (six patients traités dont un patient décédé EI Busulfan)

	HGB_206 Lovocel	Drepaglobe βAS3	BCH-BB694	CTX-001 Exacel	RUBY Renicel	BEACON BEAM-101
Nb de patients	35	4	6 (dt un 7ans)	46	28	6
Nb de cycle mobilisation	2 (1-4)	1	1	2 (1-6)	1?	1 (n=3), 2 (n=3)
Nb d'échec prod	0	0	0	8 ?	0	0
Durée aplasie PNN/Pl	20 J / 36 J	25 J/ 34J	22 J / 33 J	27 J /34,5 J	23 J / 25 J	17J / 20 J
VOE	0 sévère / 2	4	2	3/36 (9)	1	NA
HbT/F Hb totale	Hb T87Q >40% 13,4g/dl	Hb AS3 20-30% 11g/dl	Hb F 20-41% 9.3-11.4g/dl	HbF 44% 13,2g/dl	HbF 48,1% 13,8g/dl	HbF >60% 11 à 18,2G/dl
Hémolyse	Oui	Oui	Oui	Oui	Oui	Oui
Médiane suivi	> 4ans	> 3ans	6-24 mois	> 2ans	9,5 mois	3 mois
EI grave	2 leucémies dans bras	2 rejets	1 patient tjs transfusé	Un décès (COVID pdt		Un décès (Bu? M4)

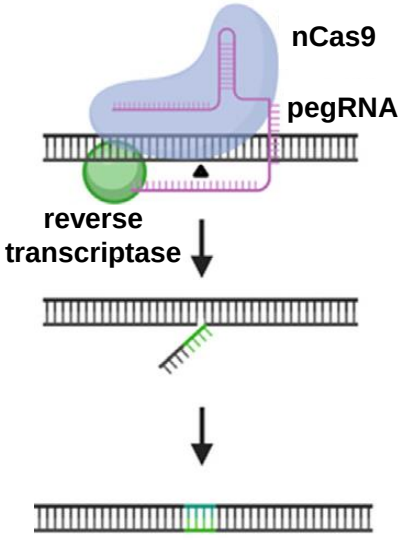
Harmonisation des définitions

	exa-cel CLIMB-121[41]	lovo-cel HGB 206[38]
VOC/VOE	Not defined/measured in trial	VOE is defined as an episode of acute pain with no medically determined cause other than a vaso-occlusion and included acute episodes of pain, ACS, acute hepatic sequestration, acute splenic sequestration, and acute priapism
Severe VOC/VOE	Severe VOC is defined as any one of the following: • Acute pain event that requires a visit to a medical facility and administration of pain medications (opioids or IV NSAIDs) or RBC transfusions • ACS, as indicated by presence of new pulmonary infiltrate associated with pneumonia-like symptoms, pain, or fever • Priapism lasting >2 hours • Splenic sequestration	Severe VOE is defined as any one of the following: • A visit to a hospital or ED that exceeded 24 hours • At least 2 visits to day unit or ED during a 72-hour period (with both visits requiring IV treatment) • Priapism episode lasting more than 2 hours and leading to a medical-facility visit

ACS: acute chest syndrome, ED: emergency department, IV: intravenous, NSAID: non-steroidal anti-inflammatory drug, RBC: red blood cell, VOC: vaso-occlusive crisis, VOE: vaso-occlusive event

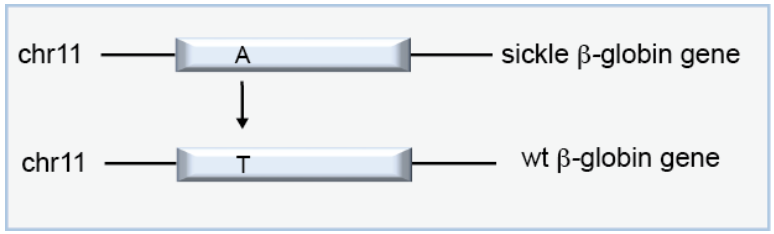
Prime editing approaches to β-hemoglobinopathies

Prime editing



all base conversions

Gene correction

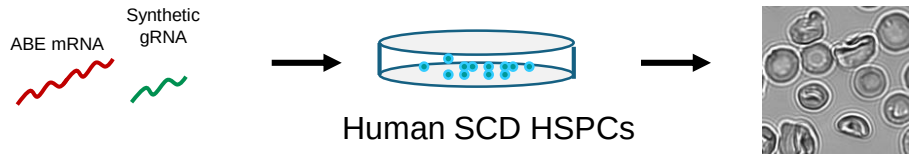


Precise correction of the SCD mutation

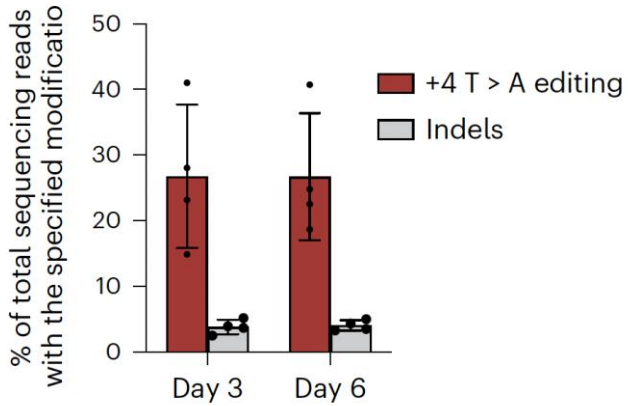
Anzalone, Nature, 2019
Li , Blood, 2023
Everette, Nature Biom Eng, 2023

Slides by A Miccio

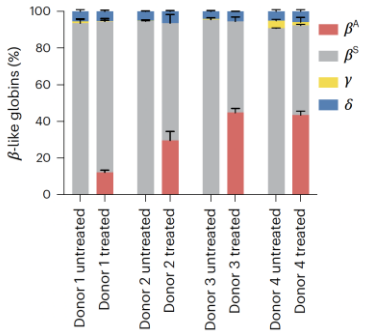
Prime editing: correction of the SCD mutation



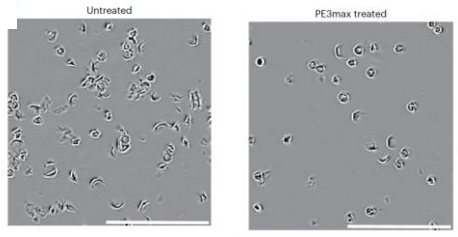
Genome editing efficiency

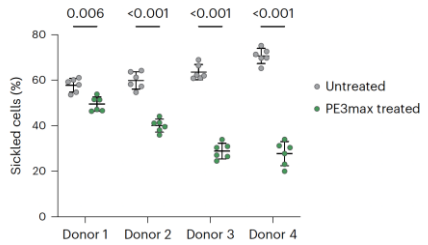


RP-HPLC (globins)



Sickling assay

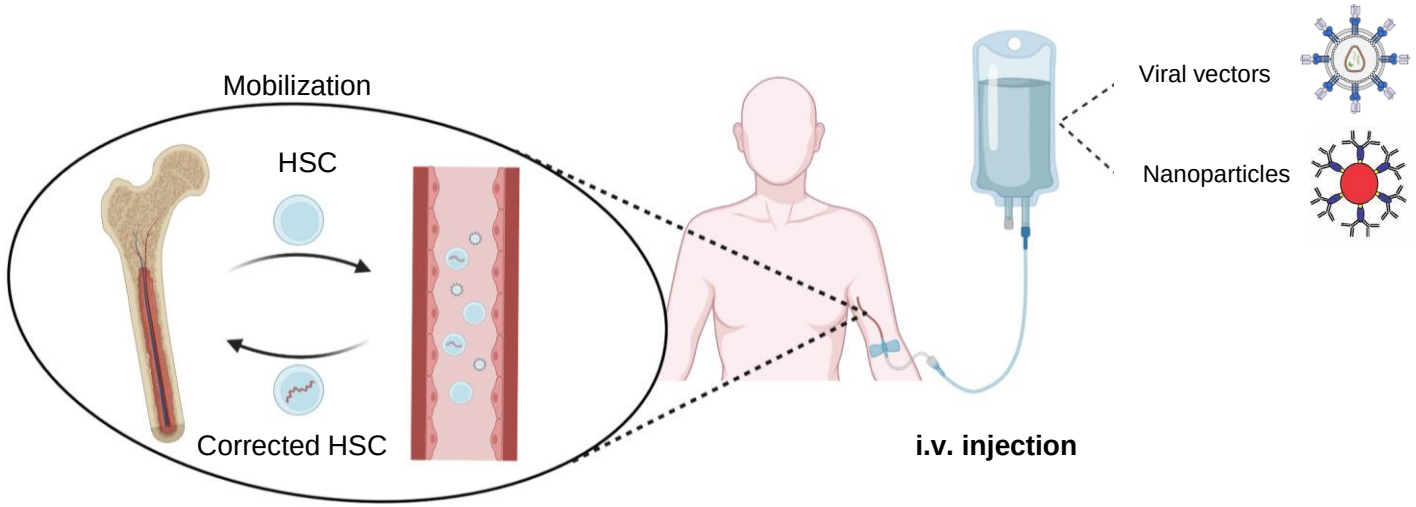




Everette, Nature Biom Eng, 2023

Slides by A Miccio

HSC-based *in vivo* gene therapy for β-hemoglobinopathies



- Less complex
- Less costly
- No conditioning

Li, Blood, 2023
Breda, Science, 2023
Lian, Nature Nanotec, 2024

Slides by A Miccio

Dimitrieviesk a et al, Blood reviews 2024

Table 1
Gene therapy and gene editing clinical trials.

Gene therapy/editing strategy				Clinical trials	Sponsors	Phase
Gene Therapy	Modified HBB delivery	Zynteglo (BB305)		NCT02151526, NCT04628585	Bluebird Bio	I, II (completed in 2019), long-term follow up (enrolling)
		Lyfgenia (BB305)		NCT02140554, NCT04293185, NCT04628585	Bluebird Bio	I, II (ongoing), III (ongoing), long-term follow up study (enrolling)
		Drepaglobe		NCT03964792	Assistance Publique - Hôpitaux de Paris	I, II (ongoing)
		βAS3-FB Vector Transduced Peripheral Blood CD34+ Cells		NCT02247843	Donald B. Kohn, M.D. (UCLA)	I, II (recruiting)
	shRNA-based gene silencing	BCH-BB694		NCT03282656, NCT05353647	David Williams, M.D. (Boston Children's Hospital)	I (ongoing), II (recruiting)
		CSL200		NCT04091737	CSL Behring	I (terminated in 2021)
	Modified anti-sickling γ-globin gene delivery	ARU-1801		NCT02186418	Aruvant Sciences	I, II (ongoing)
	Zinc Finger Nuclease (ZFN)	PRECIZN-1		NCT03653247, NCT05145062	Sangamo Therapeutics	I, II (ongoing), long-term follow up study (enrolling)
Gene Editing	Crispr-Cas systems	Crispr-Cas9	CTX001	NCT03745287, NCT04208529	Vertex Pharmaceuticals and CRISPR Therapeutics	I, II, III (ongoing), long-term follow up study (ongoing)
			GPH-101	NCT04819841	Graphite Bio	I, II (terminated in 2023)
			OTQ923	NCT04443907, NCT06155500	Novartis Pharmaceuticals	I, II (ongoing), long-term follow up study (not yet recruiting)
			CRISPR_SCD001	NCT04774536	UCSF	I, II (ongoing)
		Crispr-Cas12a	EDIT-301	(RUBY) NCT04853576	Editas Medicine	I, II (recruiting)
	Adenine Base Editor (ABE)	BEAM-101		(BEACON) NCT05456880	Beam Therapeutics	I, II (ongoing)
Allogeneic hematopoietic stem cell transplant (HSCT), gene therapy/editing				(COALESCE) NCT05153967	Vanderbilt University Medical Center	Long-term follow up study (recruiting)

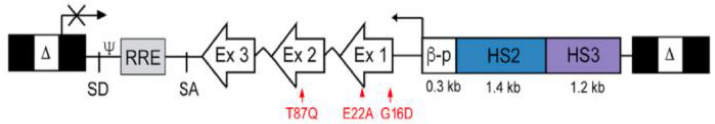
Bifunctional LVs for gene therapy of β-hemoglobinopathies

Gene Addition

+

Gene Silencing

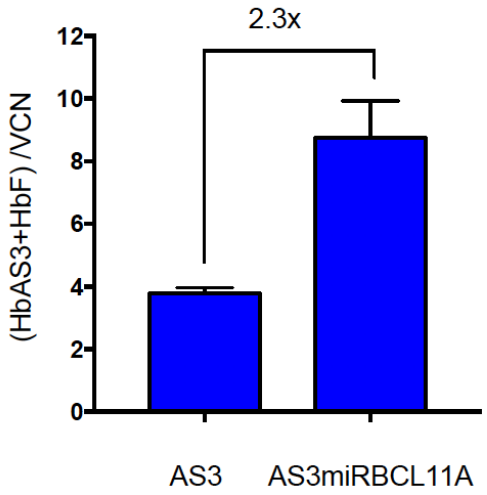
Expression of a potent **anti-sickling β-globin transgene** βAS3

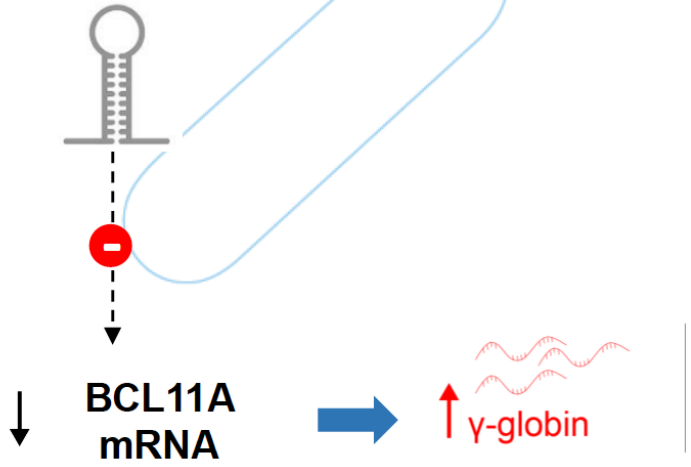


AS3 transgene

Weber et al., MTMCD 2018

Expression of an artificial **microRNA**





Bifunctional LVs double the levels of therapeutic globins in RBCs

Coût…..et disponibilité

Bbird bio : 2.8 Millions de D

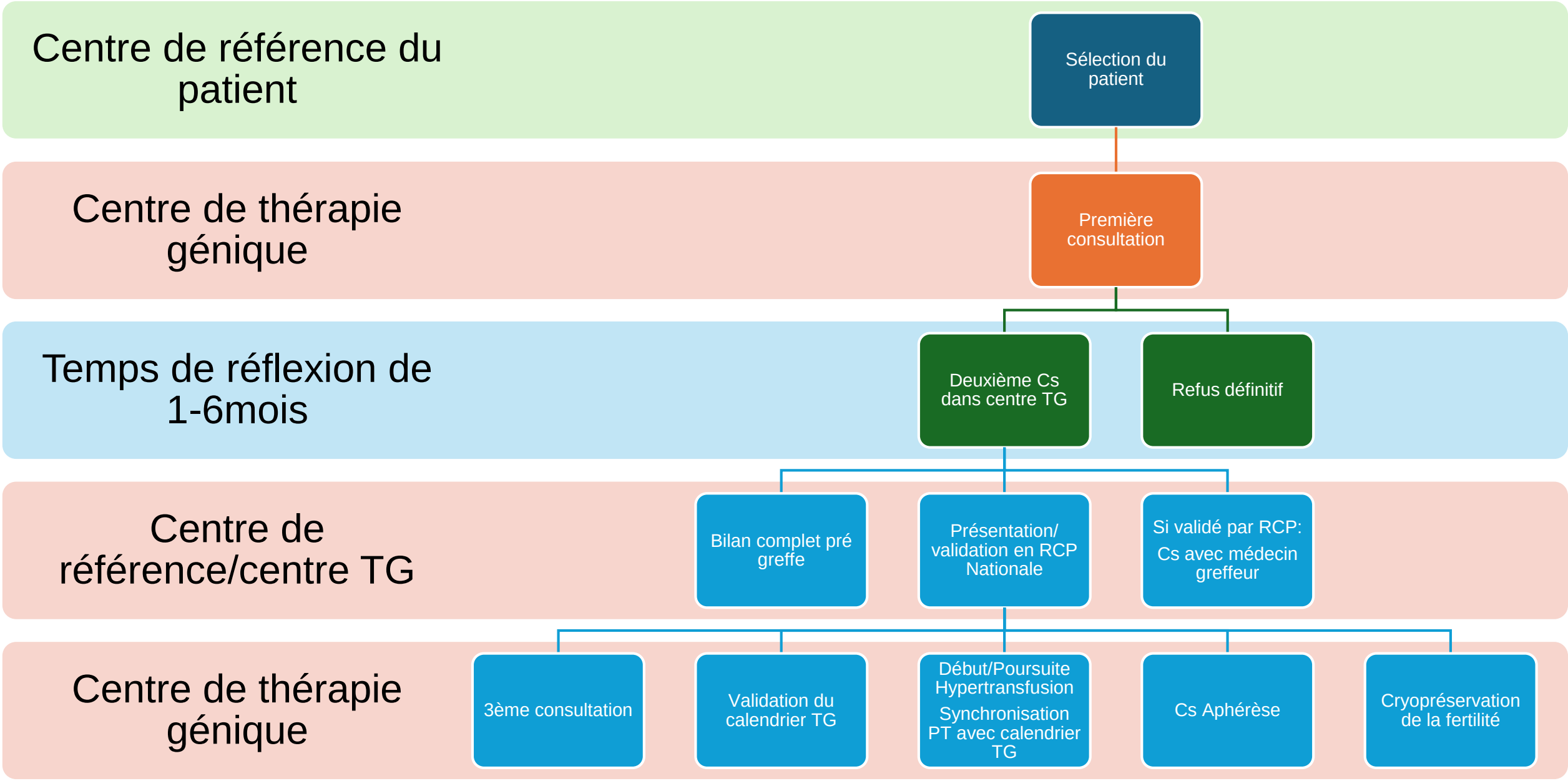
Non disponible en Europe

Vertex : 2 Millions d’Euros

13/02/2024 accord EMA

28/08/24 ASMR IV, pas de remboursement

Greffe 350 000 - 450 000 Euros


Centre de référence du patient
Centre de thérapie génique
Temps de réflexion de 1-6mois
Centre de référence/centre TG
Centre de thérapie génique
Sélection du patient
Première consultation
Deuxième Cs dans centre TG
Refus définitif
Bilan complet pré greffe
Présentation/ validation en RCP Nationale
Si validé par RCP:
Cs avec médecin greffeur
3ème consultation
Validation du calendrier TG
Début/Poursuite Hypertransfusion
Synchronisation PT avec calendrier TG
Cs Aphérèse
Cryopréservation de la fertilité

Parcours d'un patient drépanocytaire en thérapie génique

Préparation greffe minimum 3-6 mois

- Transfusion
- Bilan pré greffe
- Myélogramme/NGS
- PEC psychologique
- PEC assistante sociale
- Patientys proposé

Aphérèse

- En hospitalisation
- Plerixafor seul
- KTC
- 3 jours pour premier cycle
- 2 jours pour les cycles suivants

Préservation fertilité

Une fois nb de cellules éditées suffisantes (>3M/Kg)

Hospitalisation en USI hématologie (6 semaines)

- Busulfan à dose myéloablative
- Chambre stérile/ flux
- Complications liées à aplasie

Suivi en HDJ jusque J100

- Suivi hebdomadaire
- Effets indésirables traitements
- +/- SSR , retour à domicile
- Régime alimentaire/ mesures hygiène
- +/- Equipe douleur

Suivi en consultation

- Médecin référent/greffeur
- Intervalle variable selon réponse et complications
- Saignées si surcharge en fer
- +/- Equipe douleur