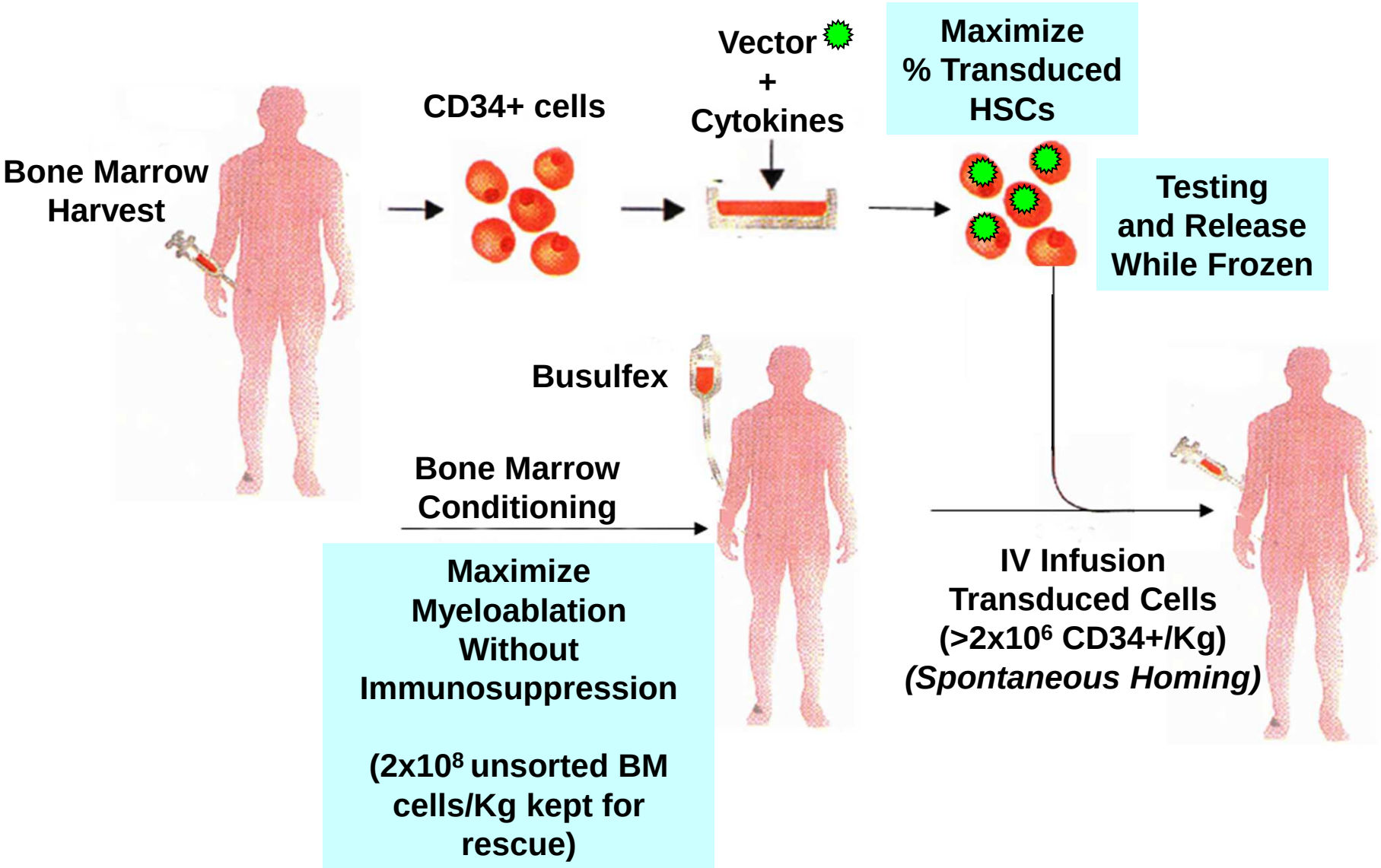
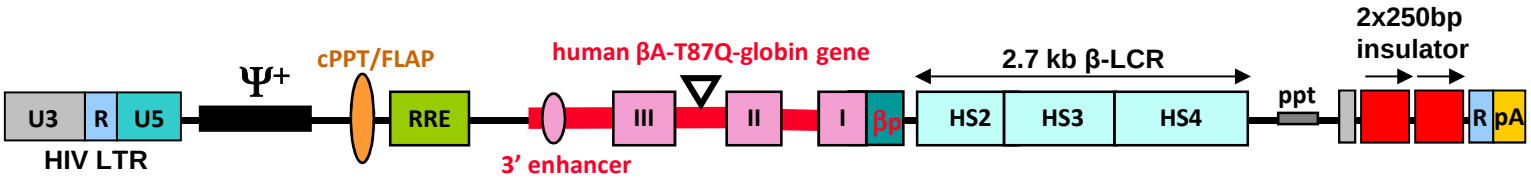
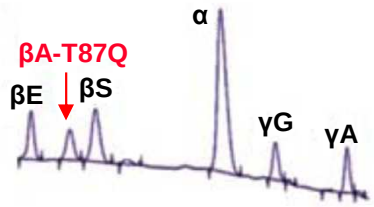
Overview of the clinical protocol



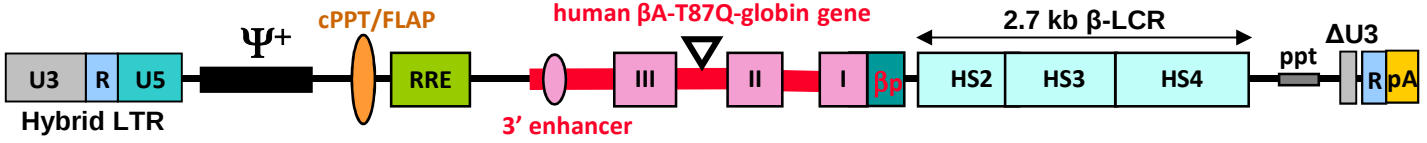
HPV569 (protocol LG001) vs BB305 (protocol HGB205)
Differences in vector's structure

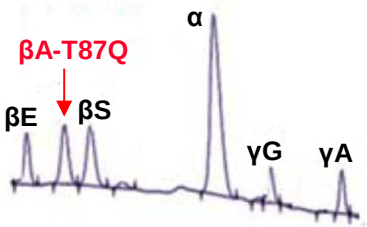
HPV569: protocol LentiGlobin LG001

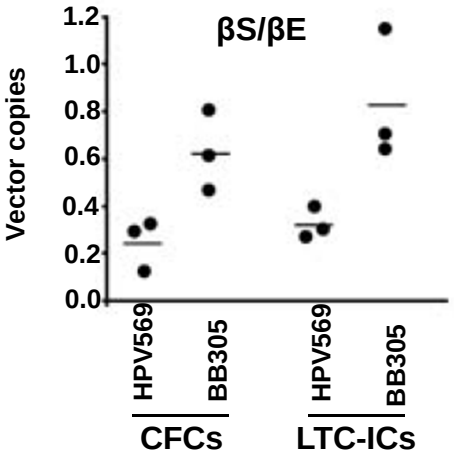


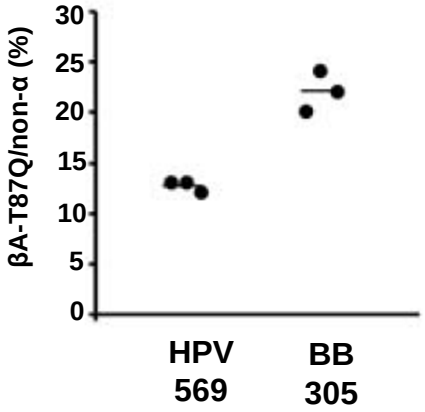


BB305: protocol LentiGlobin HGB205









O.Negre et al., Current Gene Therapy 2015

Hematological characteristics after gene therapy in lentiglobin protocols: β-Thalassemia Major Subjects

	Subject 1201	Subject 1202	Subject 1203	Subject 1206
Genotype	β0/βE	β0/βE	β0/β0	β0/βE
Neutrophil engraftment	Day + 13	Day + 15	Day + 28	Day + 16
Platelet engraftment	Day + 17	Day + 24	Day + 24	Day + 18
Non-laboratory ≥ Grade 3 Serious Adverse Events	•Mucositis •Premature menopause •Herpetic gingivostomatitis •Wisdom tooth infection	•Mucositis	•Mucositis	•Mucositis •Diarrhea (grade 2) •Vomiting (grade 1)
Number of infused CD34+ (10^6/Kg)	8.9	13.6	8.79	15.1
Months needed for Hbβ^{AT87Q} stabilisation after gene therapy	4.5	6	NA	NA
g/dL of Hbβ^{AT87Q} at the stabilisation after gene therapy	7.1 - 7.3	9 - 9.5	NA	NA

Characteristics of subject with severe sickle cell disease (1204)

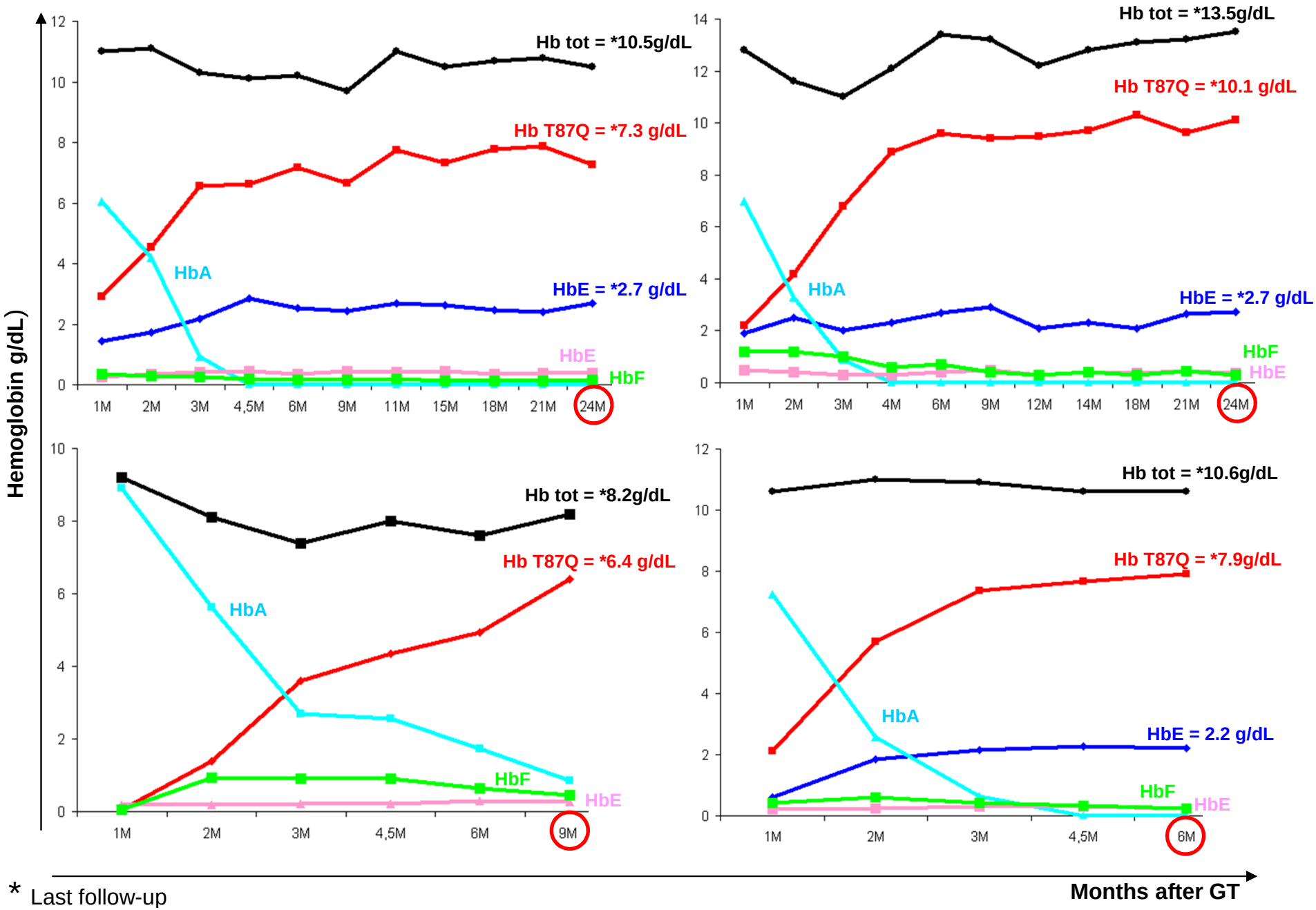
Indication for transplant	Age at Consent	Sex	Genotype	pRBC Transfusion Requirement (mL/kg/year)[a]	Cell source	$CD34^+$ VCN in Drug Substance[b]	$CD34^+$ Cell Dose ($x10^6$/kg)	Follow-up
• **Multiple VOCs** • **ACS[c]** • **Silent cerebral infarct**	13	Male	β^S/β^S	170	Bone marrow	1.2 / 1.0	5.6	6M

[a] *mean pRBC requirement per year, over the past 2 years prior to consent*
[b] *VCN= number of vector copies per diploid genome*
[c] *ACS=acute chest syndrome*

Clinical safety for infused subject

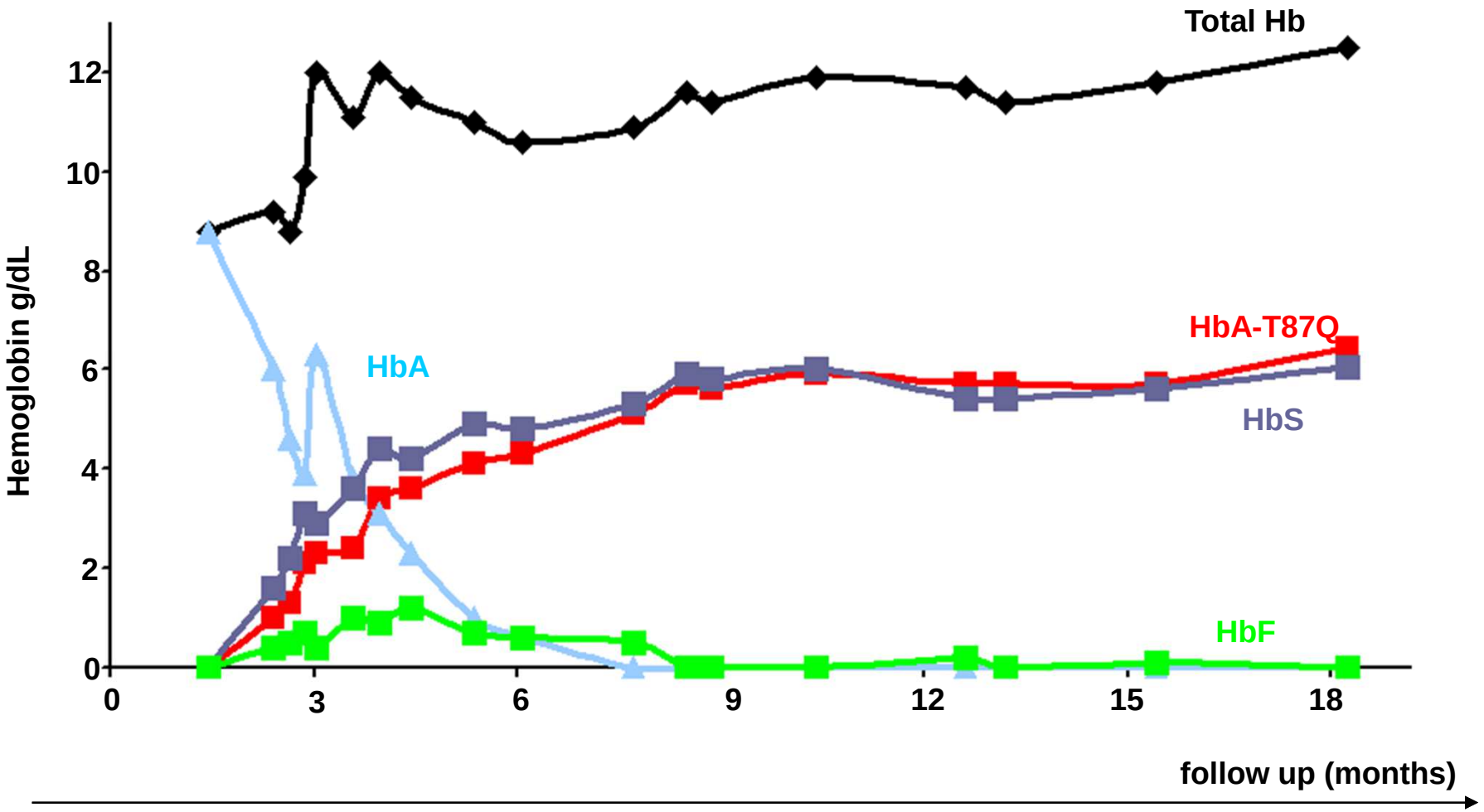
	Subject 1204
Genotype	β^S/β^S
Neutrophil engraftment	Day + 37
Platelet engraftment	Day + 91
Non-laboratory ≥Grade 3 AEs	None
SAEs post-infusion	None

Globin-chains detection after gene therapy by HPLC



* Last follow-up

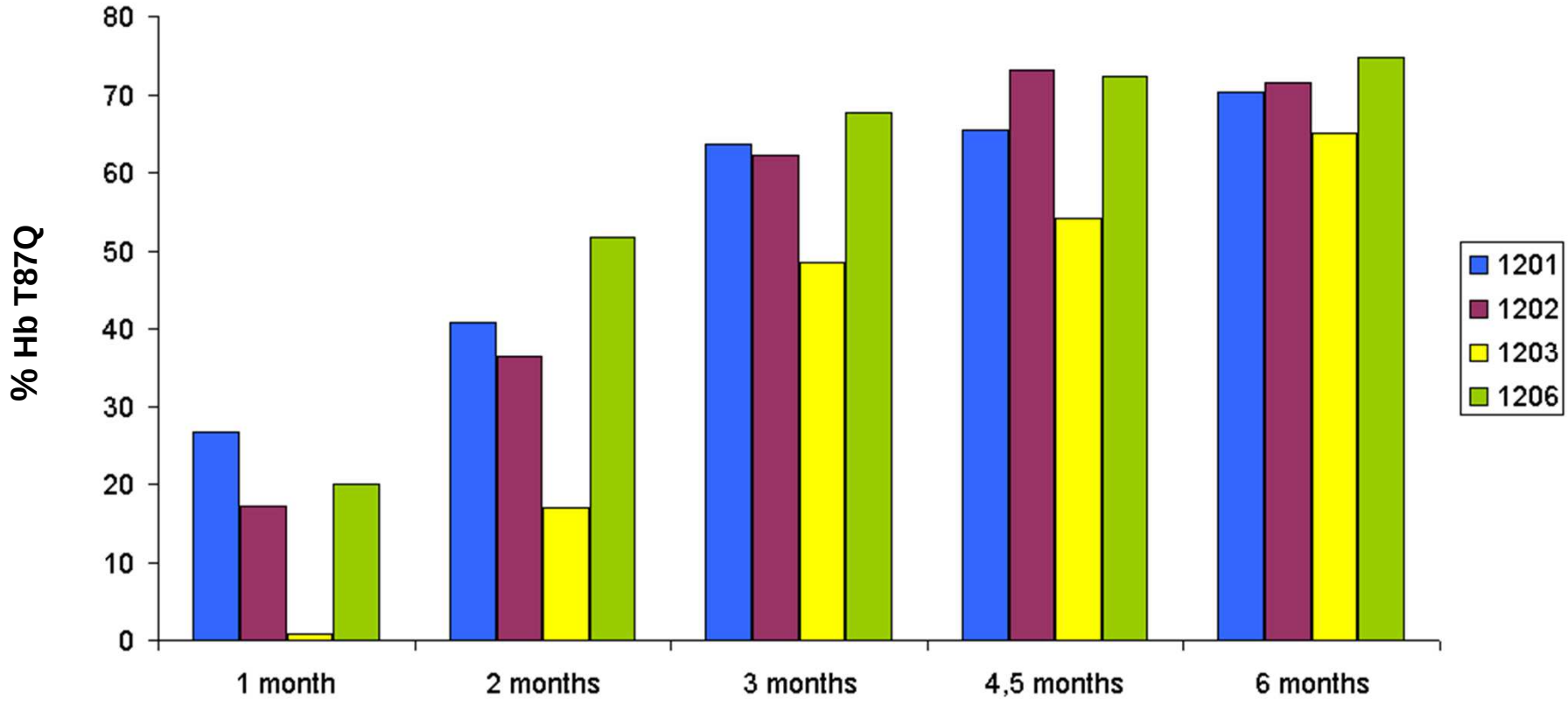
Globin-chains detection after gene therapy by HPLC: SCD patient



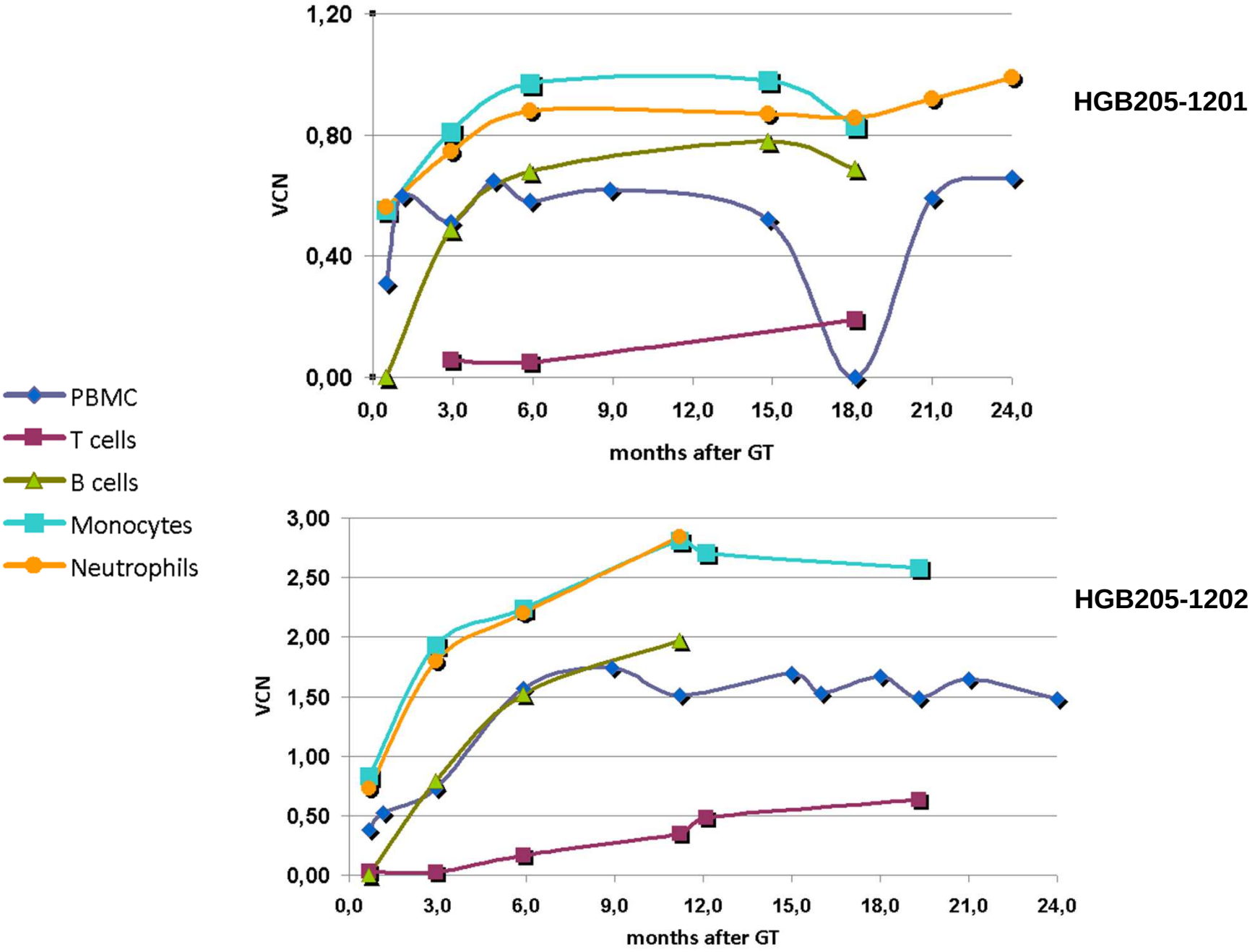
18 months: 12.5 g/dL of Hb tot and 6.4 g/dL of Hb T87Q!

Necker's results by RP-HPLC

% of HbT87Q at the same time point after gene therapy

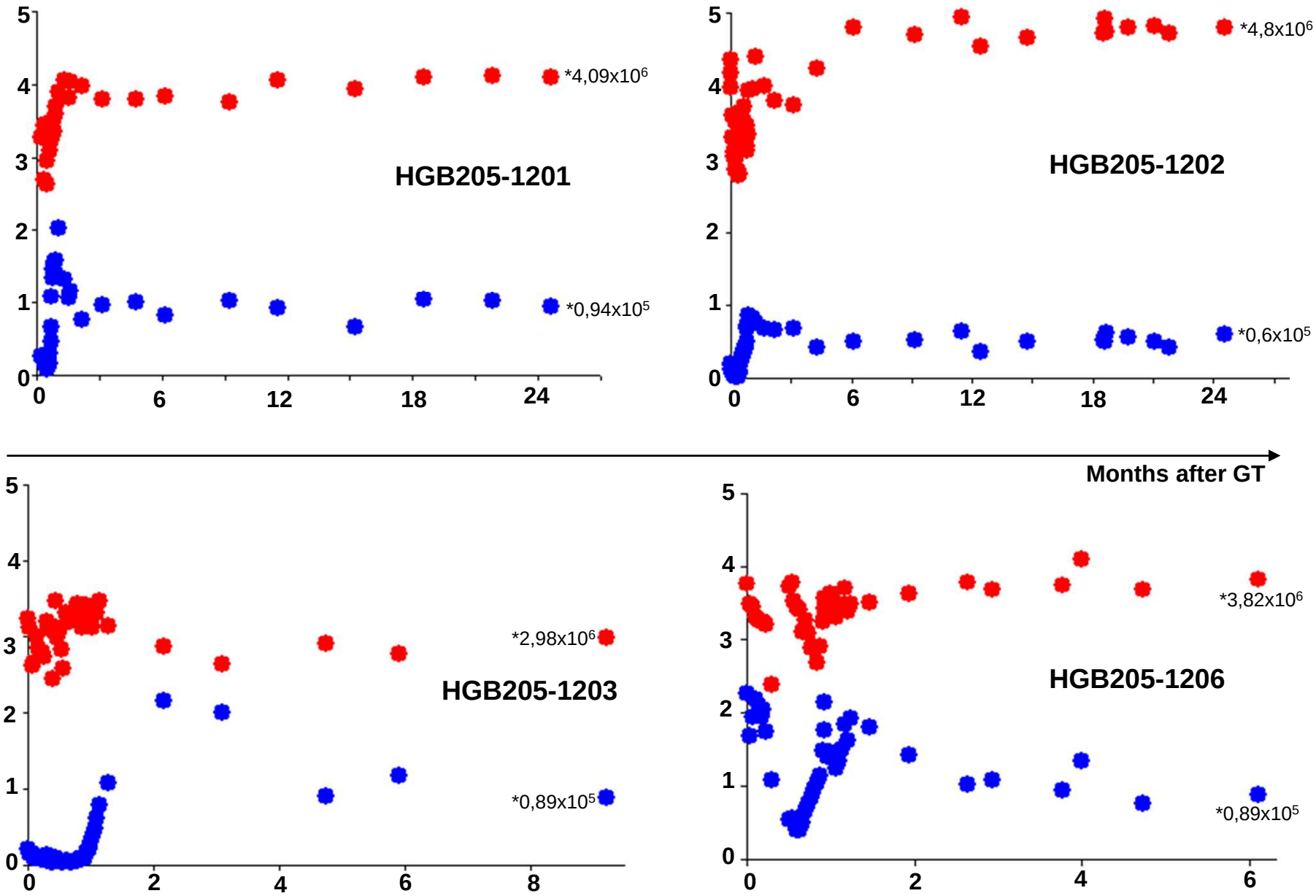


Vector copy number in the subpopulations: 1201 and 1202

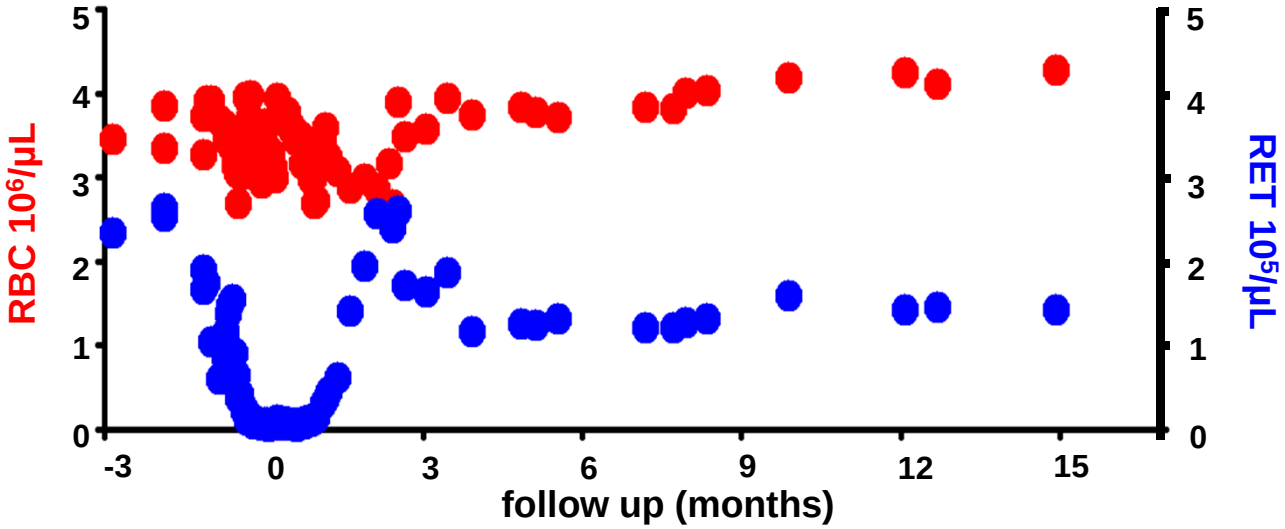


Red blood cells (x10^6/µL)
Reticulocytes (x10^5/µL)

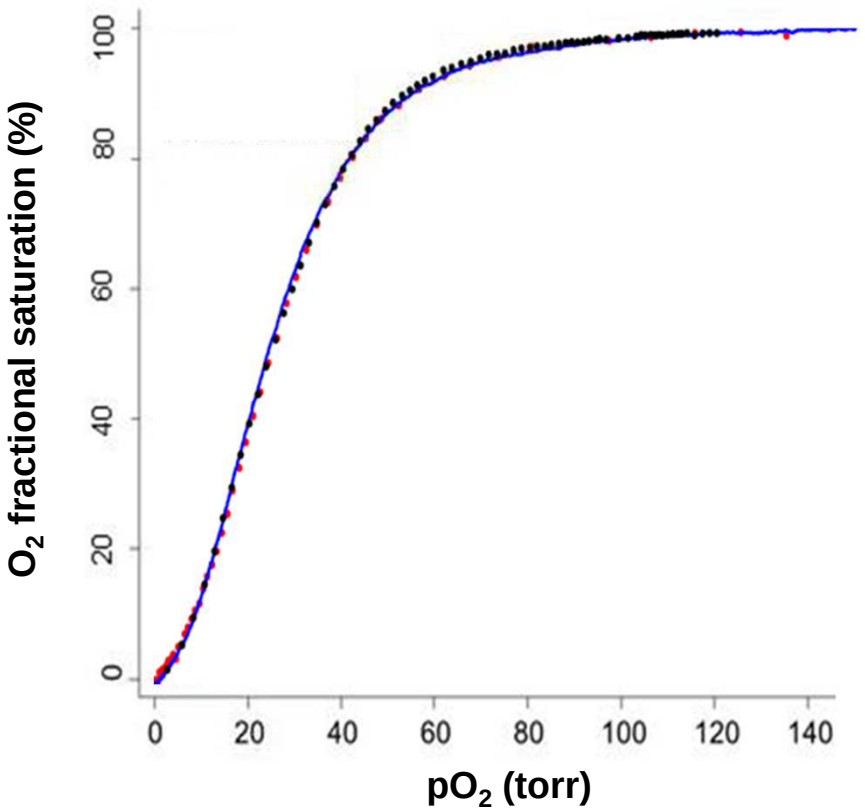
Correction of dyserythropoiesis

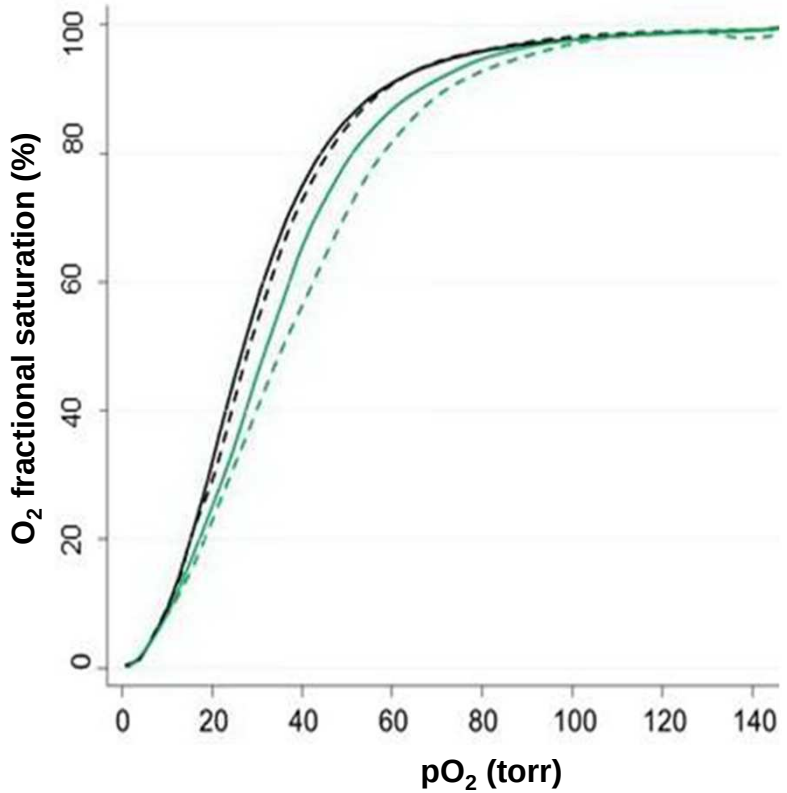


Correction of dyserythropoiesis in the SCD patient



SCD patient's oxygen dissociation curve
at 12 months of follow-up is similar to asymptomatic heterozygote





Deoxygenation

Reoxygenation

Subject 1204 deox

Subject 1204 reox

Subject 1204's mother

Normal subject

Untreated SCD

Severe SCD Subject 1204: Improvement in clinical status and hemolytic markers at 12 months

	Pre-Treatment	1 Year After Treatment
Transfusions	Chronic transfusions	**Weaned off transfusions** Last transfusion on Day + 88 (> 9 months ago)
Clinical Status	Multiple hospitalizations before starting transfusion regimen	**No hospitalizations or acute SCD-related events**
Hemolysis	Baseline reticulocyte count 238.3 x 10^9/L and LDH 626 U/L while on transfusions	• **Reticulocytes 143.1 x 10^9/L** • **LDH 274 U/L**

Preliminary Conclusions

- Both the HGB-205 (France) and HGB-204 (US) studies demonstrate continued promise of gene therapy with LentiGlobin BB305 Drug Product in β-thalassemia major

- Early results with gene therapy with LentiGlobin BB305 Drug Product show sufficient vector-derived hemoglobin production to reduce or eliminate transfusion requirements

- The safety profile is consistent with autologous transplantation, without gene-therapy related adverse events, and with tri-lineage engraftment and polyclonal reconstitution

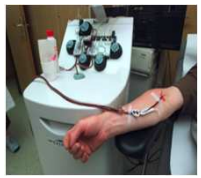
- HGB-205 (France) shows promising data in the first subject with severe sickle cell disease treated with gene therapy with positive clinical signs and production of anti-sickling hemoglobin (**45%**, and still increasing) at 6 months well above the threshold (30%) that may show meaningful therapeutic effects

Coût de la thérapie génique

aujourd'hui et demain

Patient + Coûts Hospitaliers + coûts de production

Recueil



Transplantation CSH

Transductio n CD34+ HSCs

Et demain ?

34 894.43 € + 19 315.60 € + 52 597.80 €

106 807.84 €

Greffe autologue CSH : 30 000 €

Greffe allogénique CSH = 100 000 €, Greffe incompatible : 350 000 et 1 000 000 €

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