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Steady Musculoskeletal Health After Gene Therapy in Severe Hemophilia A: 5-Year Results

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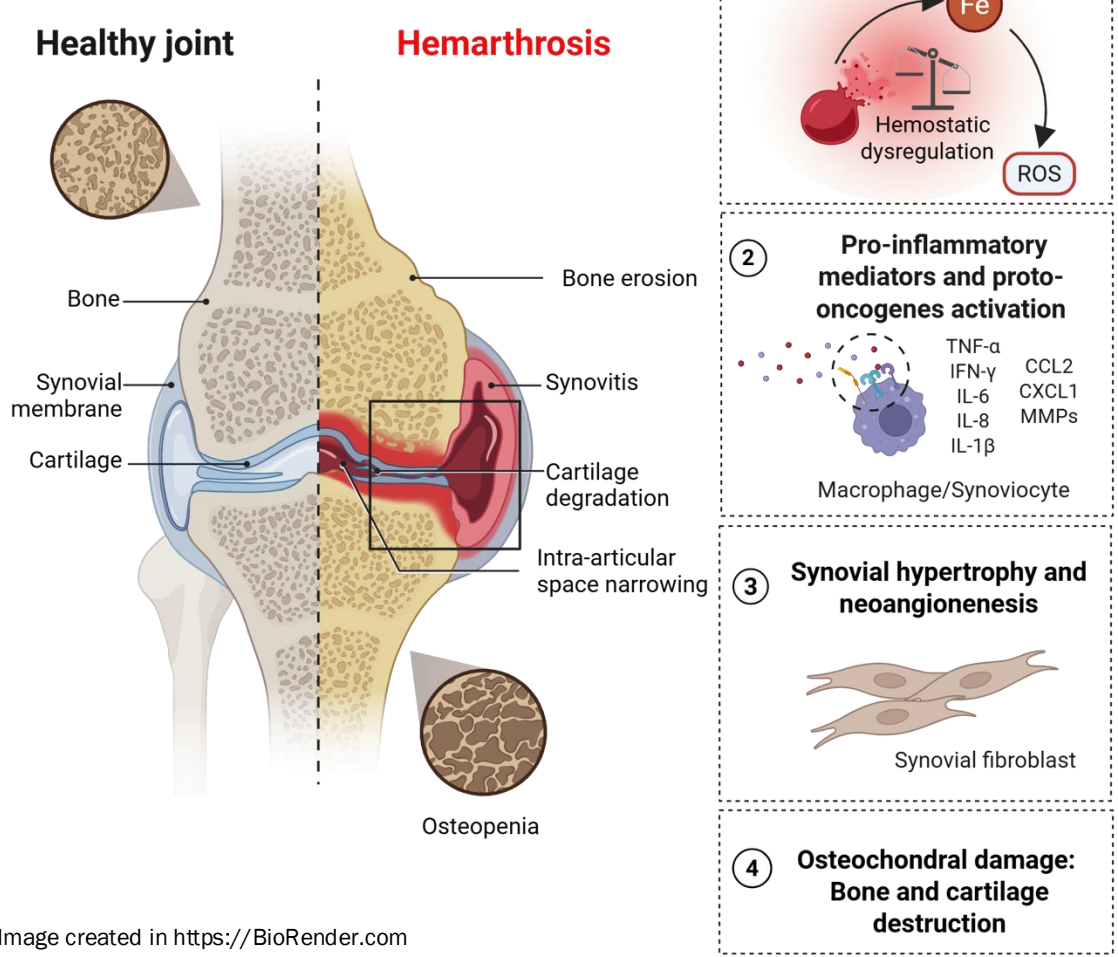
Presentation Learning Objectives

At the conclusion of this presentation, participants will be able to:

1. Understand the long-term effects of valoctocogene roxaparvovec gene therapy on musculoskeletal (MSK) health in patients with severe hemophilia A (sHA)

2. **Identify** the clinical and biomarker-based measures used to assess joint health and inflammation following gene therapy in sHA

3. **Interpret** the significance of stable joint health scores and changes in inflammatory and bone metabolism biomarkers over a five-year follow-up period post-gene therapy



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Gene therapy may provide **stable factor VIII expression**

↓

What happens to musculoskeletal health?

16 patients with severe hemophilia A
Single infusion of $6x10^{13}$ vg/kg of valoctocogene roxaparvovec
from August to November, 2019

HJHS
MSK physical evaluation

FISH
HAL
Functioning evaluation

HEAD-US
Ultrasound joint evaluation

Plasma biomarkers*
Inflammation
Extracellular matrix degradation
Bone metabolism
Cell migration and neoangiogenesis

Baseline, Year 1, Year 2, Year 3, Year 4, Year 5

*Plasma biomarkers: (1) inflammation: IL1β, TNFα, IL17a, IL6; (2) extracellular matrix degradation: LOX1, MMP1, MMP3, MMP9, MMP13; (3) bone metabolism: RANKL, OC, SOST, calcitonin, Dkk1, SDF1α; (4) cell migration and neoangiogenesis: MIP1α, VCAM, P-selectin, E-selectin, VEGFα, SDF1α

HJHS: Hemophilia Joint Health Score; HAL: Haemophilia Activities List; FISH: Functional Independence Score in Hemophilia; HEAD-US: Hemophilia Early Arthropathy Detection with Ultrasound

Clinical characteristics

	n=16
Age (years) – median (range)	**26.5** (19-41)
Masculine – n (%)	16 (100)
Race/ethnicity – n (%)	
White	8 (50)
Black	5 (31.2)
Indigenous	3 (18.8)
BMI (kg/m^2) – mean (range)	**26.1** (16.2-34.5)
Comorbidities – n (%)	
Previous hepatitis C	**1 (6.2)**
Previous hepatitis B	**1 (6.2)**
Previous inhibitor	0
HIV infection	0
FVIII prophylaxis	16 (100)

BMI: body mass index; HIV: human immunodeficiency virus; FVIII: factor VIII

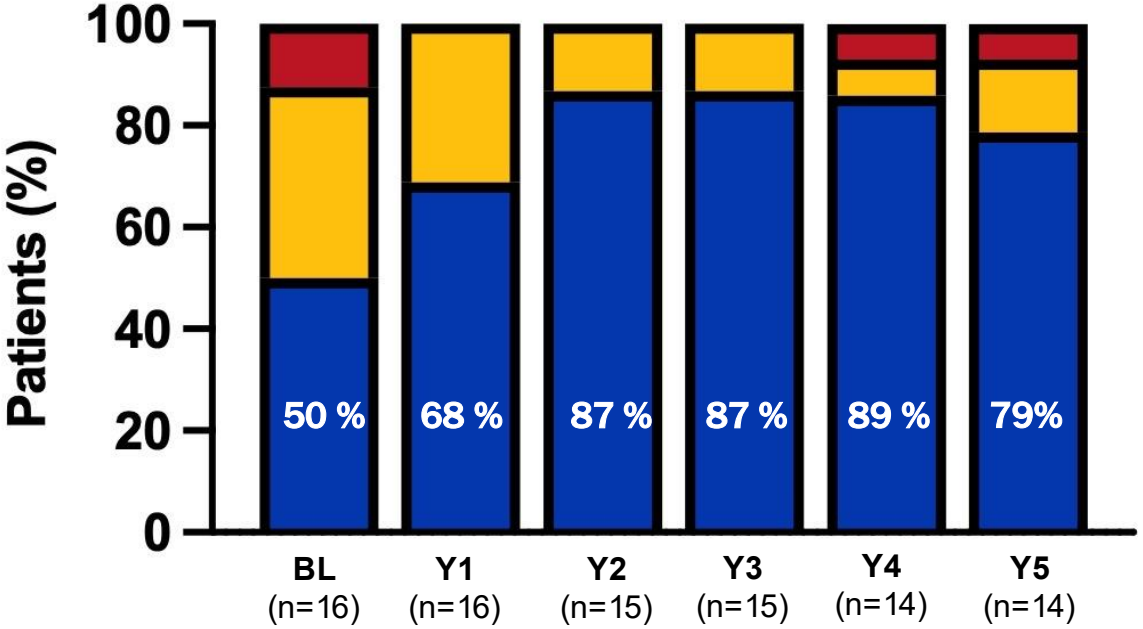
MSK health at baseline

	n=16
Annual bleeding rate (episodes/year) Median (range)	0.5 (0-5)
Annual joint bleeding rate (episodes/year) Median (range)	0 (0-2)
Target joints – n (%)	0
Affected index joints* – n (%)	71 (84)
HAL – median (IQR)	82.8 (70.4-99)
FISH – median (IQR)	28 (22-32)
HJHS total score – median (IQR)	47 (25.5-61.7)
HEAD-US – median (IQR)	25.5 (14-36.7)

* Affected joints were defined by joint HJHS score of ≥ 2

MSK: musculoskeletal health; HJHS: Hemophilia Joint Health Score; HAL: Haemophilia Activities List; FISH: Functional Independence Score in Hemophilia; HEAD-US: Hemophilia Early Arthropathy Detection with Ultrasound; IQR: interquartil range

Annual bleeding rates



7 patients (50%) with zero bleeds over 5 years

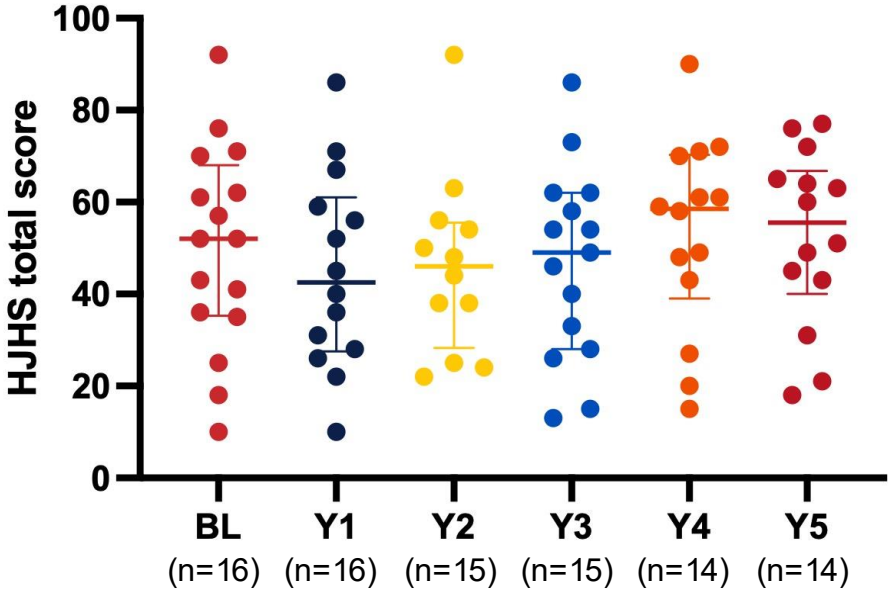
2 patients (12.5%) resumed FVIII prophylaxis (W68 and W180)

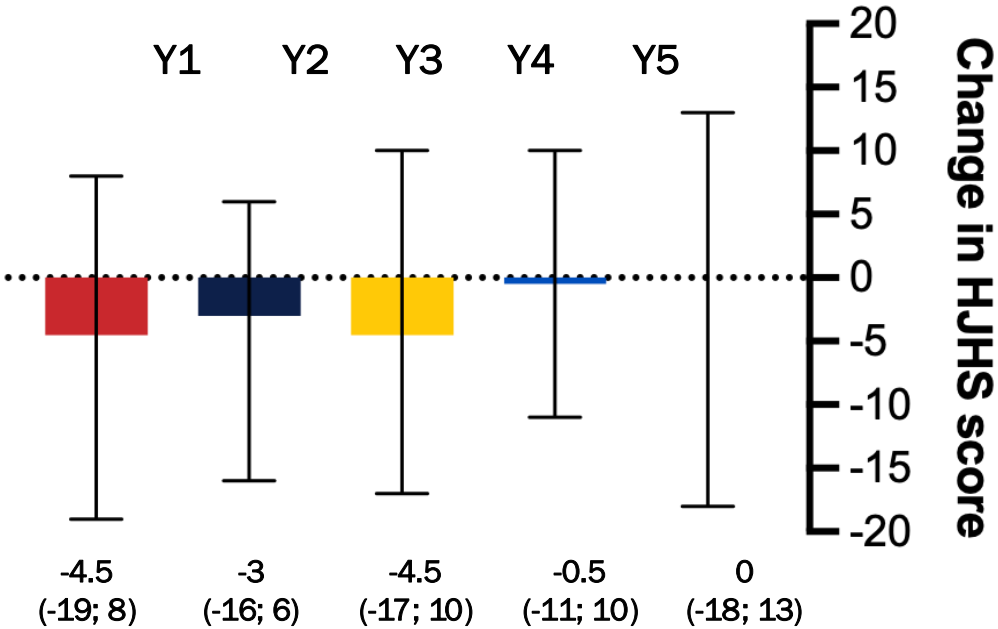
Median ABR (range)

BL	Y1	Y2	Y3	Y4	Y5
0.5 (0-5)	0 (0-2)	0 (0-1)	0 (0-1)	0 (0-14)	0 (0-4)

Joint physical exam – HJHS

Maximum HJHS global score: 124





No difference between HJHS scores at baseline and years 1-5

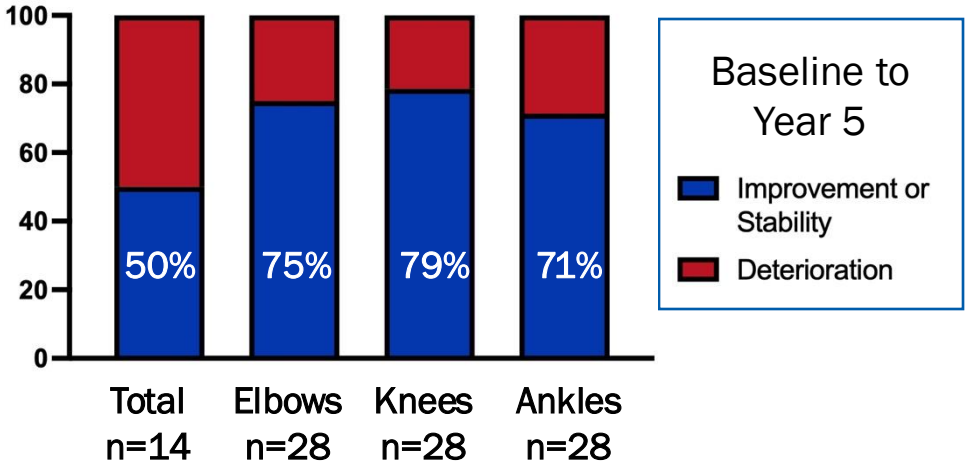
Minimal Clinically Important Difference:
4 for global score
2 for each joint[1]

Friedman 2-way analysis of variance by ranks

1. Kuijlaars IAR, et al. *Haemophilia*, 2017

HJHS single joint scores

Maximum HJHS single joint score: 20



24 joints (28%) with an increase of ≥2 on joint HJHS

Minimal Clinically Important Difference:
4 for global score
2 for each joint[1]

22 joints (26%) had minimal or absent impairment (score <2) at baseline

7 (32%) joints with progression at Y5

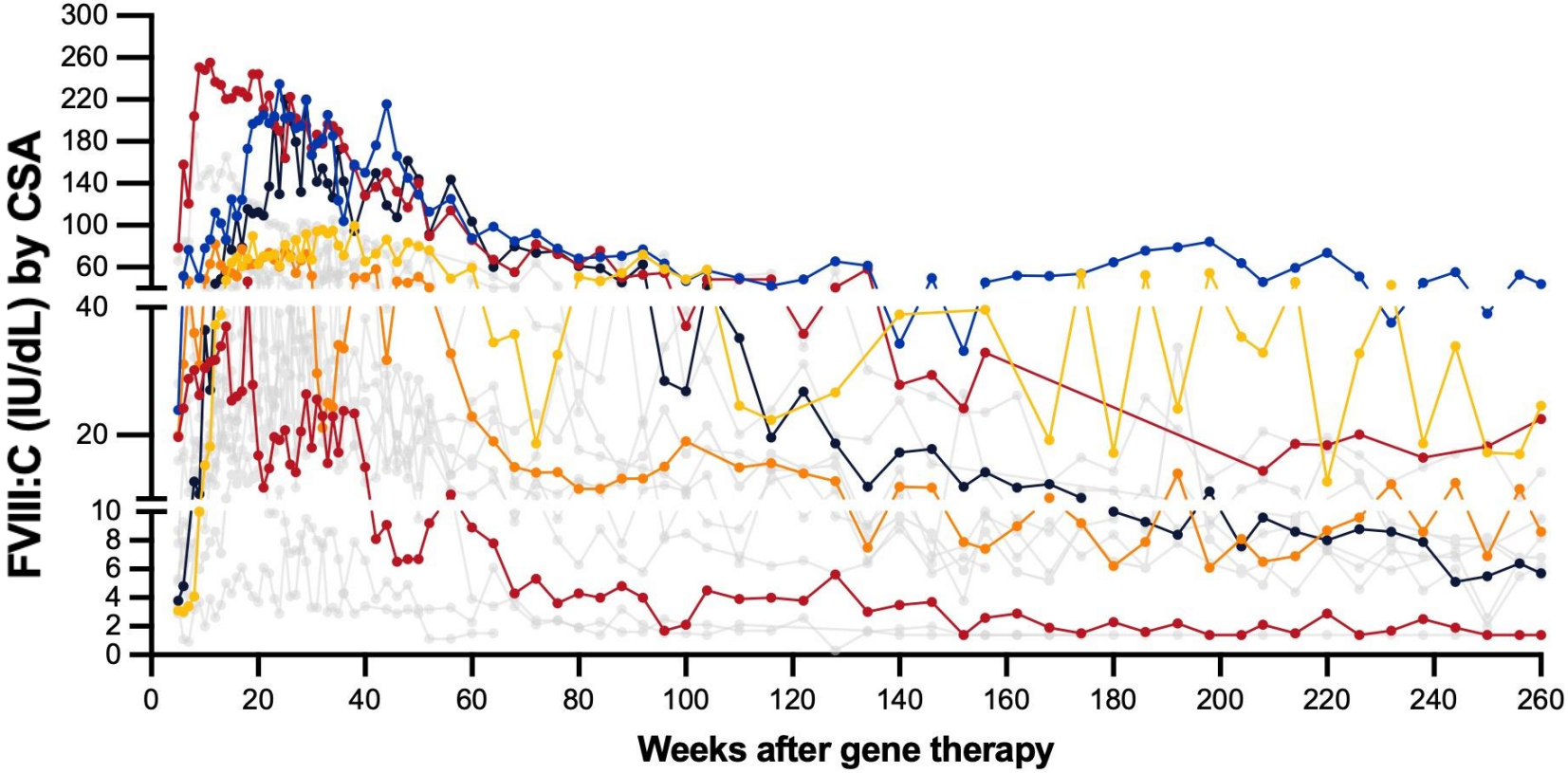
5/7 had zero bleeds during 5y FUP

At Y5, 5 other joints with improvement

At Y5, 20 joints (23%) with minimal or absent impairment

1. Kuijlaars IAR, et al. *Haemophilia,* 2017

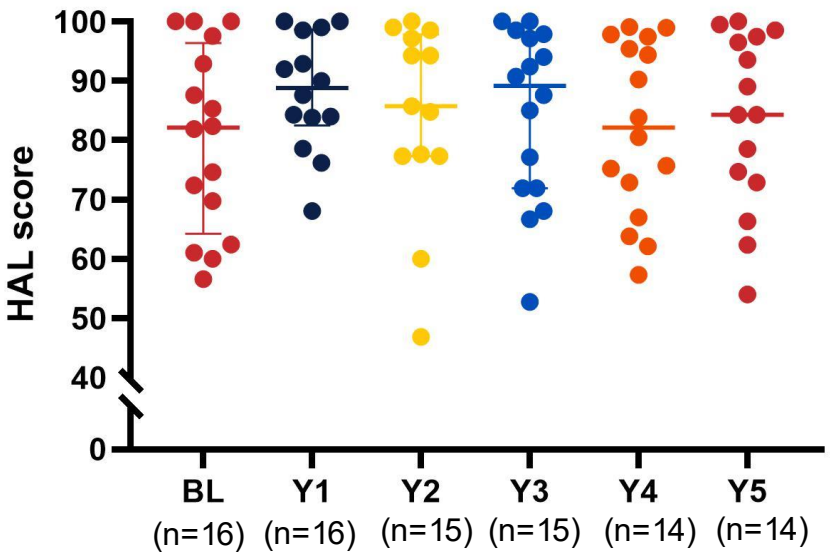
FVIII:C in increased HJHS at Year 5 (n=7, 50%)



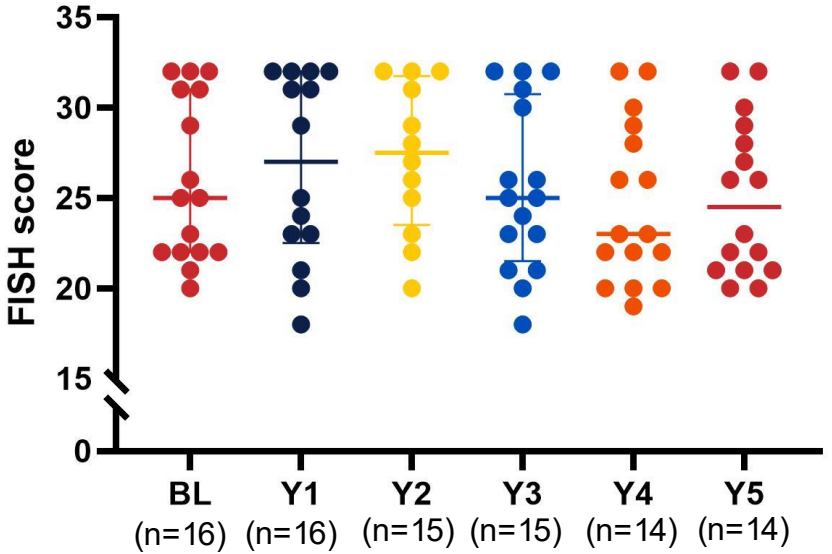
CSA: chromogenic substrate assay

Functionality

HAL score



FISH score

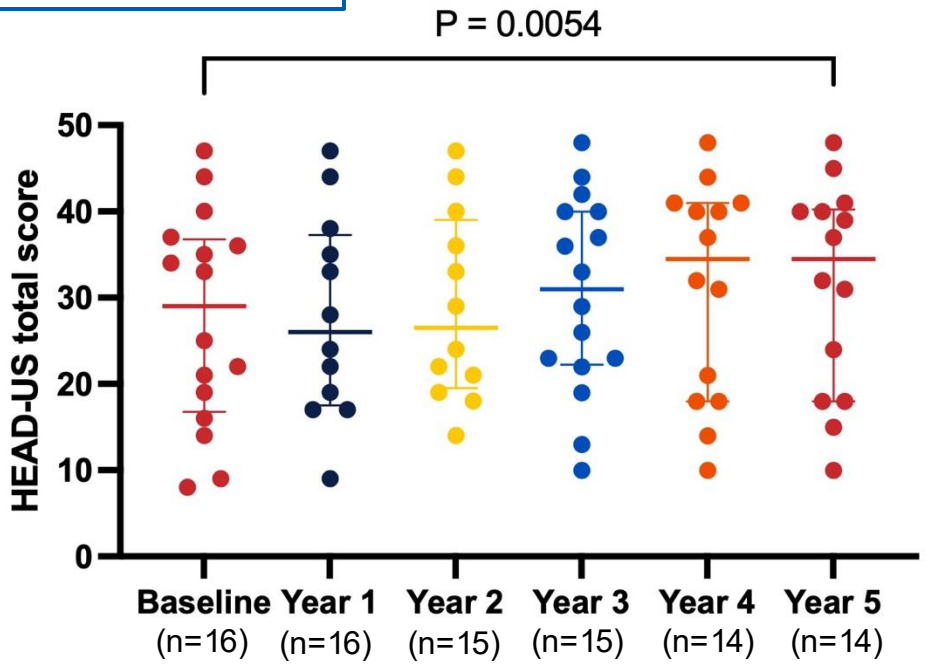


No difference between HAL and FISH scores at baseline and years 1-5

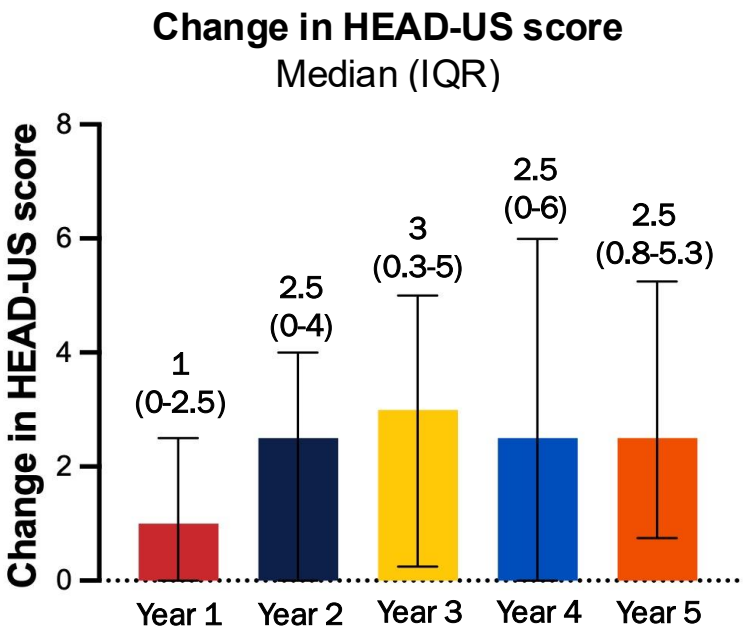
Friedman 2-way analysis of variance by ranks

Ultrasound evaluation - HEAD-US

Maximum HEAD-US score: 48



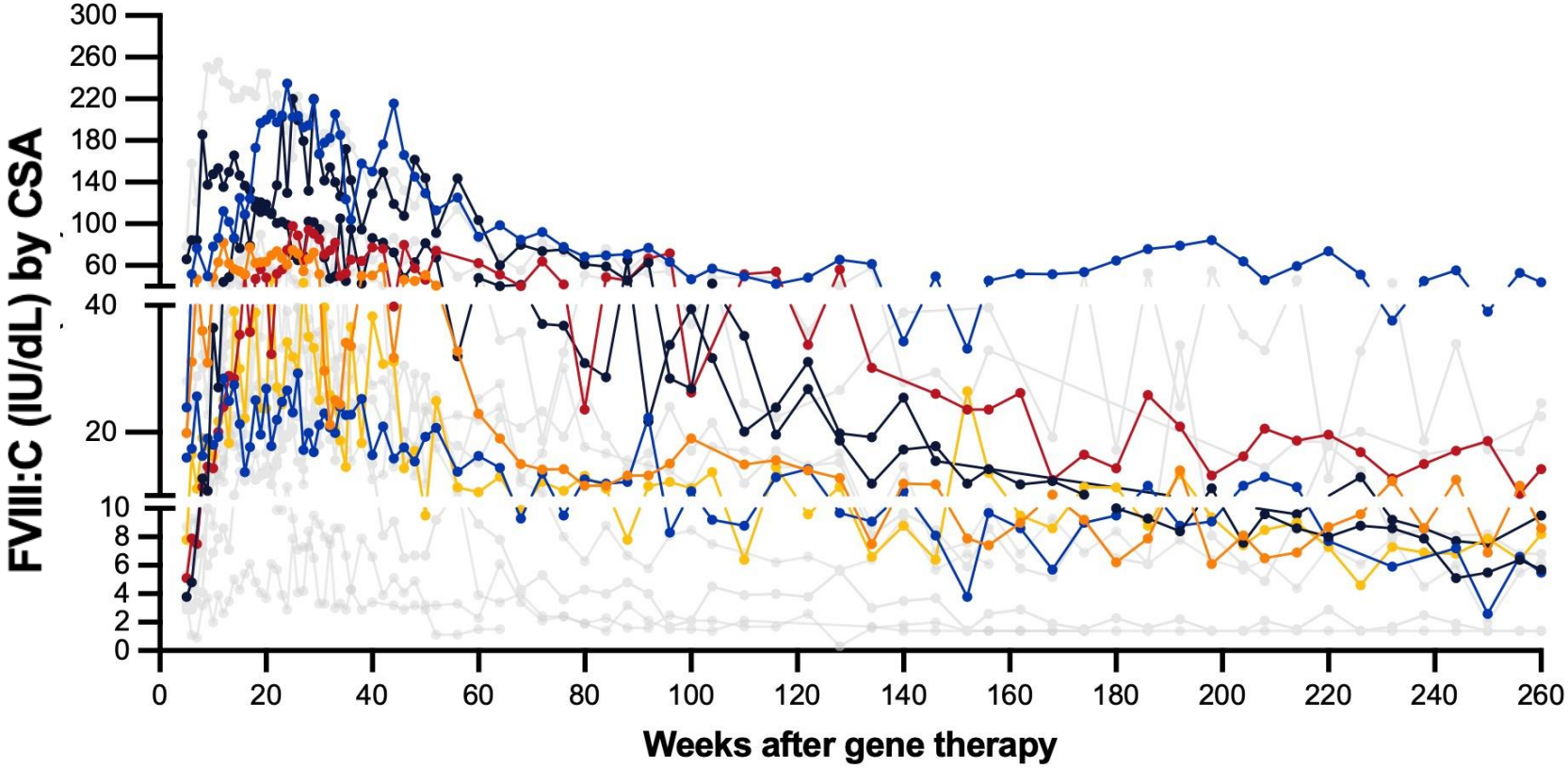
HEAD-US	Baseline	Year 5
Median (IQR)	29 (16.8-36.8)	34 (18-40.3)



Comparing baseline and Year 5:
7 (**50%**) patients with **stable** HEAD-US scores

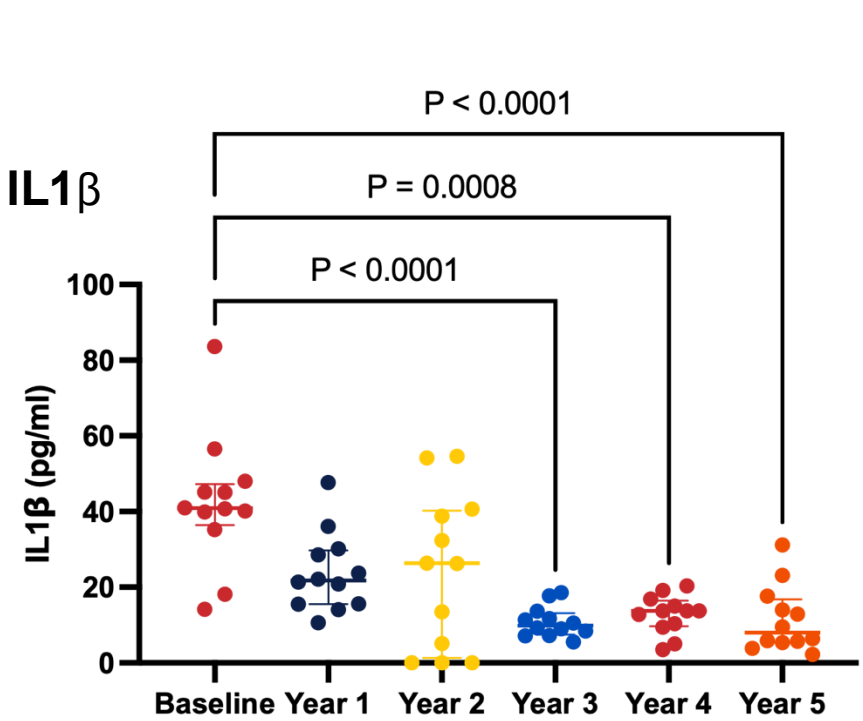
Friedman 2-way analysis of variance by ranks, *post-hoc* analysis with Wilcoxon signed rank test

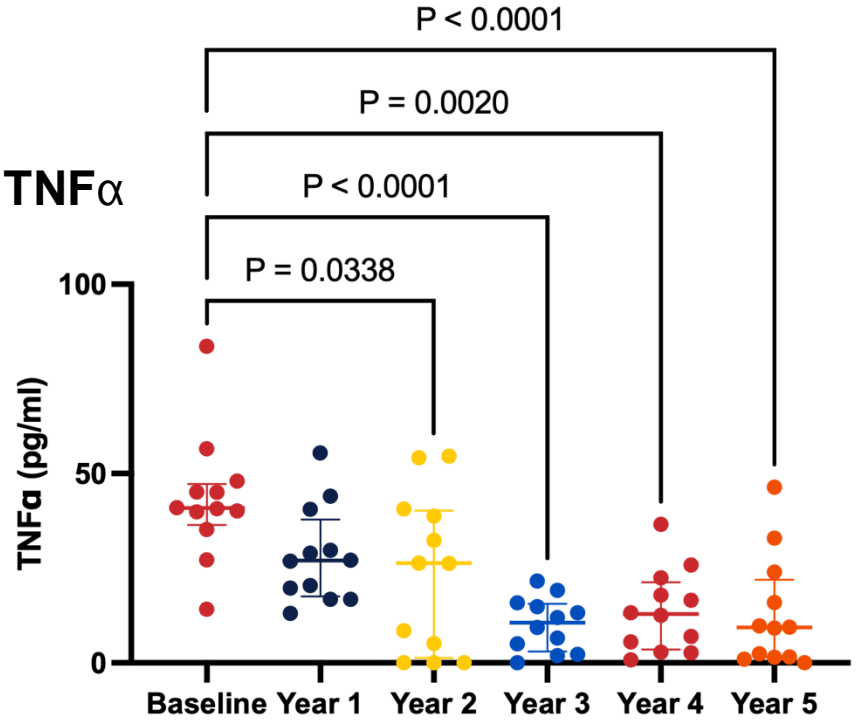
FVIII:C in increased HEAD-US at Year 5 (n= 7, 50%)



CSA: chromogenic substrate assay

Reduction in plasma IL1β and TNFα suggests a decrease in inflammatory state

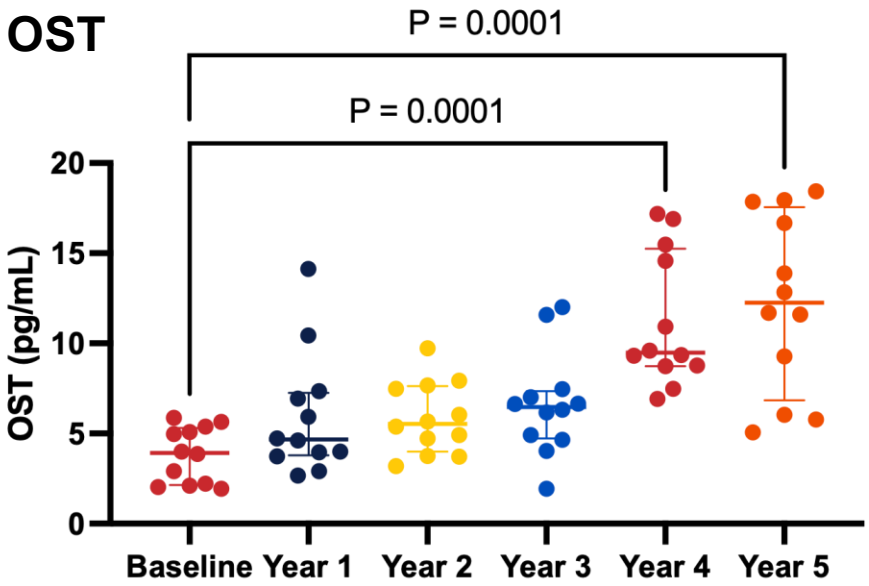


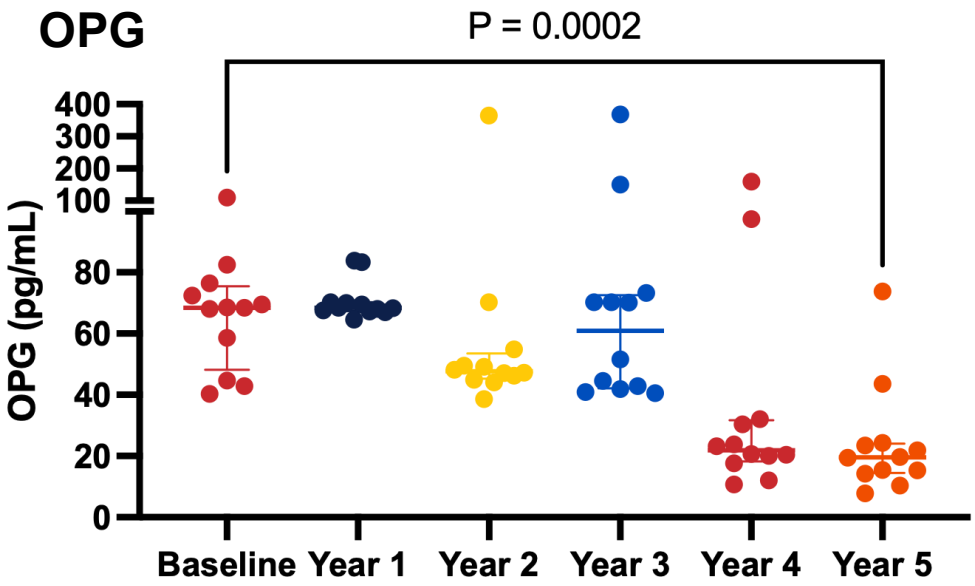


Friedman 2-way analysis of variance by ranks

Increased osteocalcin (OST) suggests **increased bone formation**

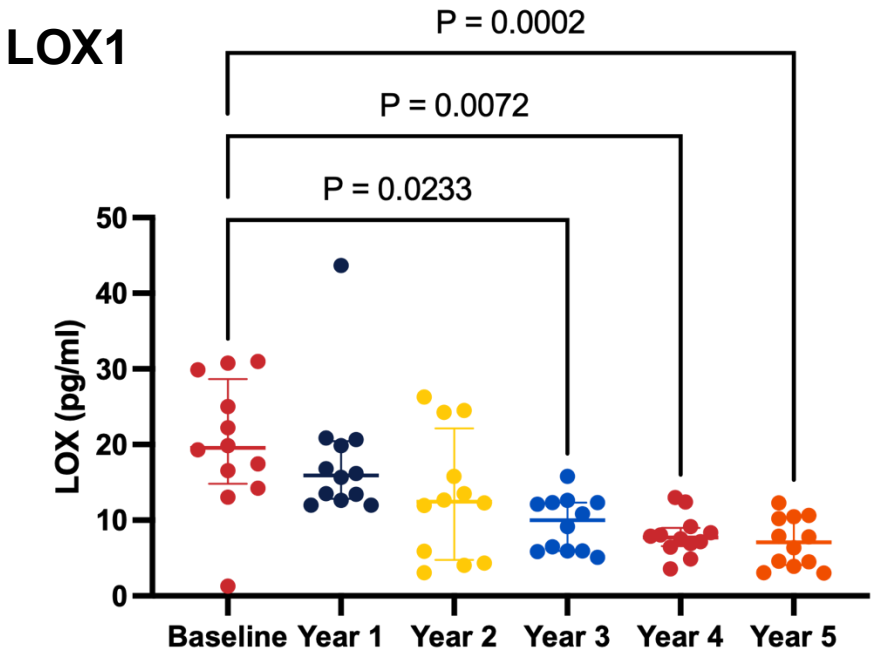
Reduced osteoprotegerin (OPG) indicates **increased bone remodelling**

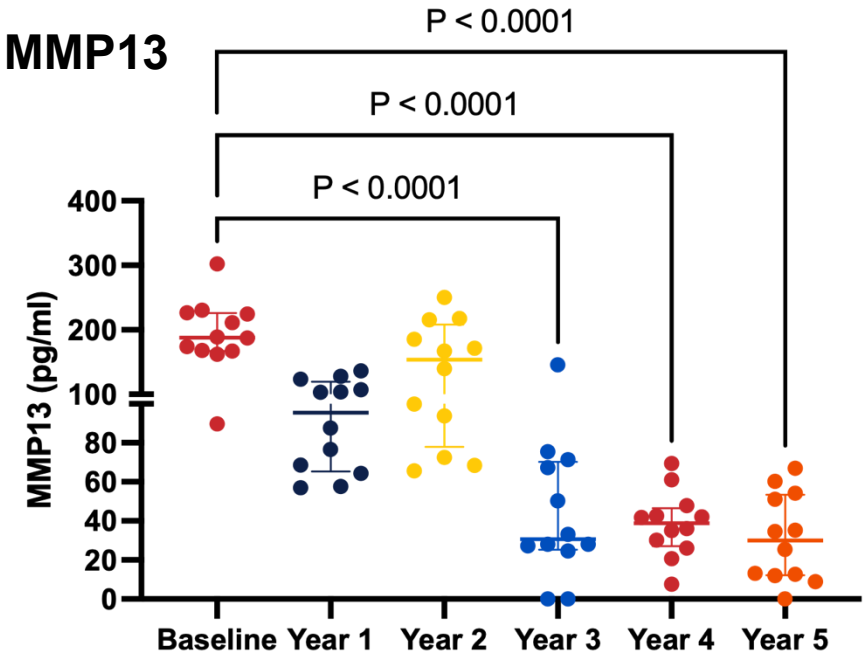




Friedman 2-way analysis of variance by ranks

Reduction in lysil oxidase 1 (LOX1) and colagenase 3 (MMP13) suggests **decreased extracellular matrix degradation**





Friedman 2-way analysis of variance by ranks

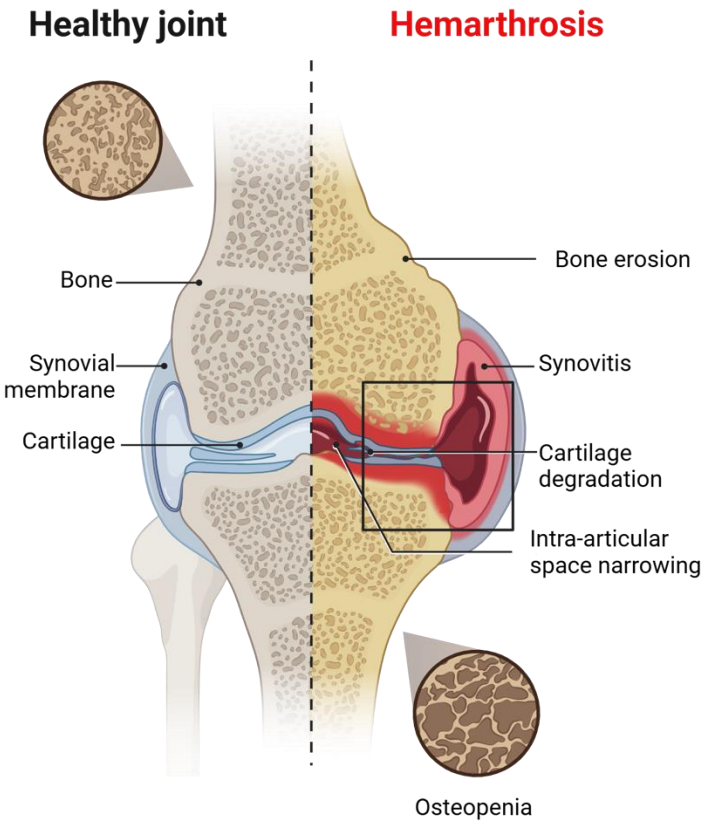
Strengths and limitations

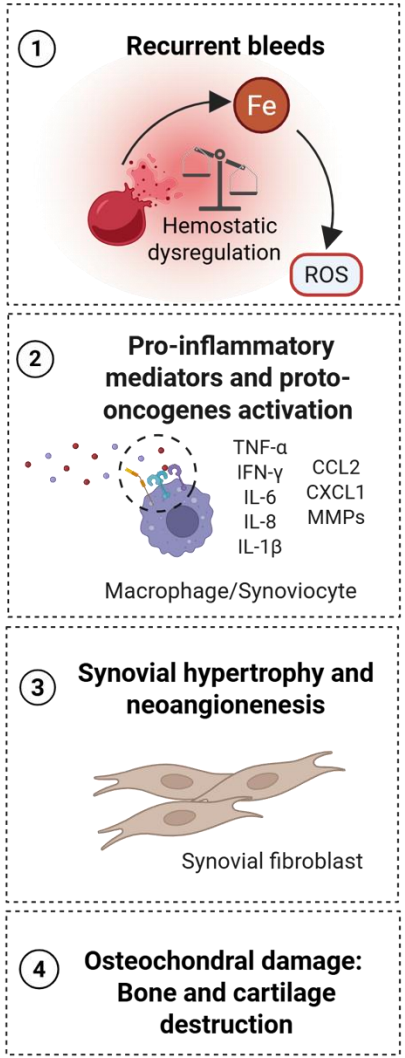
STRENGTHS

- **Longest prospective MSK follow-up** after gene therapy
- **Meaningful number** of patients treated with gene transfer
- **Multimodal** MSK assessment

LIMITATIONS

- **Small cohort**
- Ceiling effect and limited sensitivity of some MSK assessment tools → **need for new tools for new therapies?**





Median ABR= 0 at Y5
79% with zero bleed in Y5
50% with zero bleed from Y1-Y5

Decreased inflammatory status
↓ plasma IL1β and TNFα

Decreased ECM degradation
↓ plasma LOX1 and MMP13

Increased bone formation and remodelling
↑ plasma OST and ↓ plasma OPG

Five years after gene therapy for hemophilia A

- **Sustained hemostatic benefit**
  - Only 2 patients resumed prophylaxis
  - ABR = 0 at Y5
- **HJHS scores remained stable**
  - Joints with minimal impairment showed clinical stability
  - Ongoing arthropathy was observed in some joints with zero bleeds
- **Ultrasound assessment showed arthropathy progression**
  - No impact on functionality
  - No correlation with FVIII expression

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