Pharmacodynamics (PD) and pharmacokinetics (PK) of dirloctocogene samoparvovec in people with severe to moderately severe hemophilia A (HA)

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Dirloctocogene samoparvovec is an investigational adeno-associated viral (AAV) vector gene therapy for which the safety and effectiveness have not been determined. Dirloctocogene samoparvovec is not approved for use in any country.

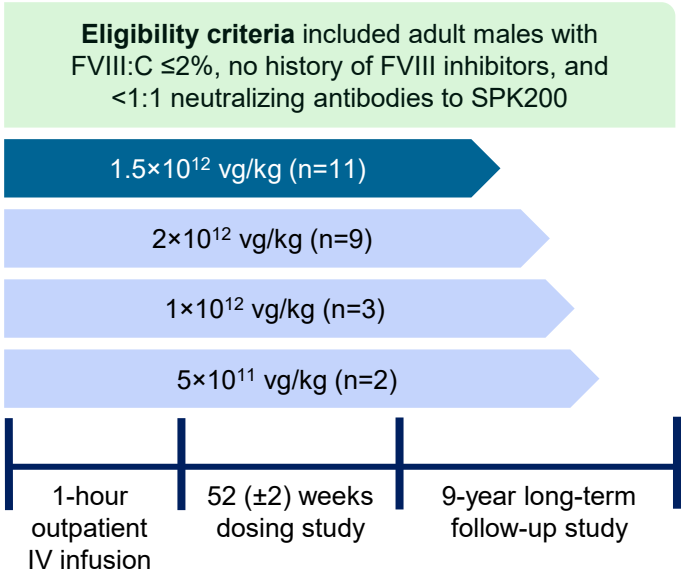
Disclosures for Lindsey George

- **Consultant/Honoraria:** CSL Behring, MyoGene Bio, Pfizer, Regeneron Pharmaceuticals Inc., and Spark Therapeutics, Inc.
- **Scientific Advisory Board:** Form Bio

Dirloctocogene samoparvovec Phase 1/2 program: low-dose AAV gene therapy for HA

- High-dose AAV gene therapy for HA has raised **uncertainties of FVIII expression durability and predictability**[1–3]
- Investigational dirloctocogene samoparvovec utilizes doses up to 60–120x lower than other HA vectors,[1,3–6] to **minimize dose-dependent AAV toxicities**
- Up to 6.5 years of follow-up at Phase 1/2, dirloctocogene samoparvovec showed a favorable safety profile and durable FVIII expression mostly **in the mild HA range**[7]
- Here we describe Phase 1/2 **PK and PD analysis** of low-dose dirloctocogene samoparvovec
  - PK: vector shedding
  - PD: peak and long-term expression range of FVIII by OSA

Phase 1/2 study design[4]
NCT03003533/NCT03432520

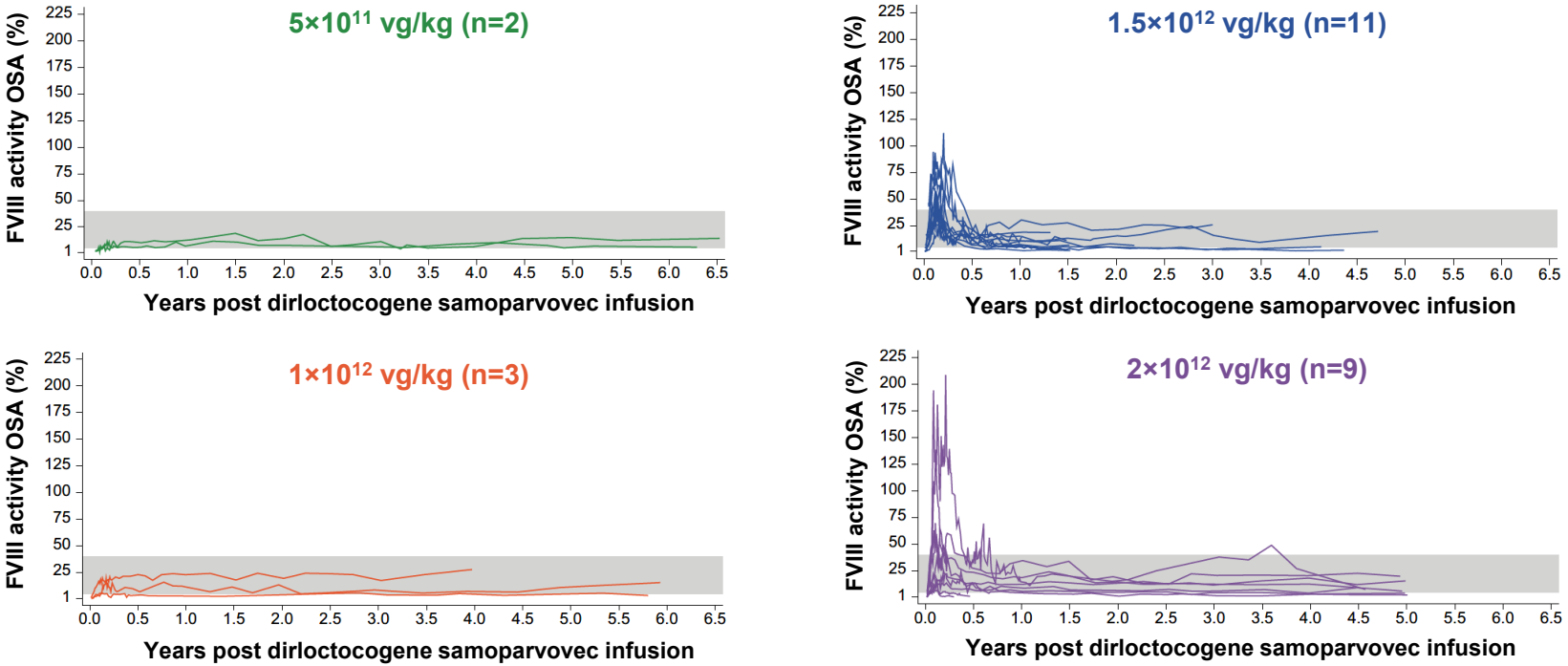


AAV, adeno-associated viral; F, factor; FVIII:C, factor VIII coagulant activity; HA, hemophilia A; IV, intravenous; OSA, one-stage assay; PD, pharmacodynamics; PK, pharmacokinetics; vg, vector genome

1. Mahlangu J, et al. N Engl J Med 2023;388:694–705; 2. Madan B, et al. J Thromb Haemost 2024;22:1880–93; 3. Leavitt AD, et al. Blood 2024;144(Suppl. 1):1053; 4. George LA, et al. N Engl J Med 2021;385:1961–73; 5. George LA, et al. THSNA 2024; 6. Chowdary P, et al. Blood 2023;142(Suppl. 1):3624; 7. George LA, et al. RPTH 2024;8(Suppl. 2):e102503

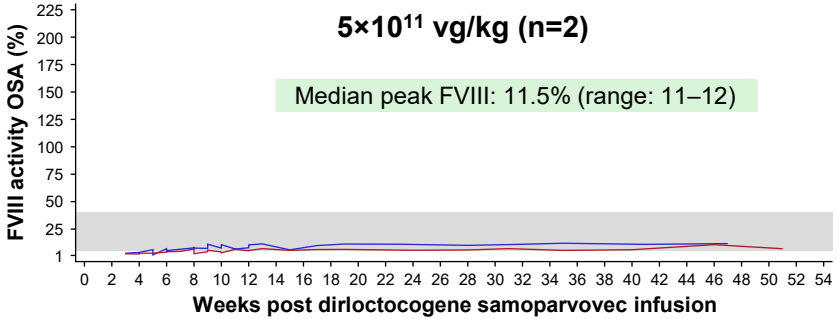
Durable FVIII expression: mild HA in most participants

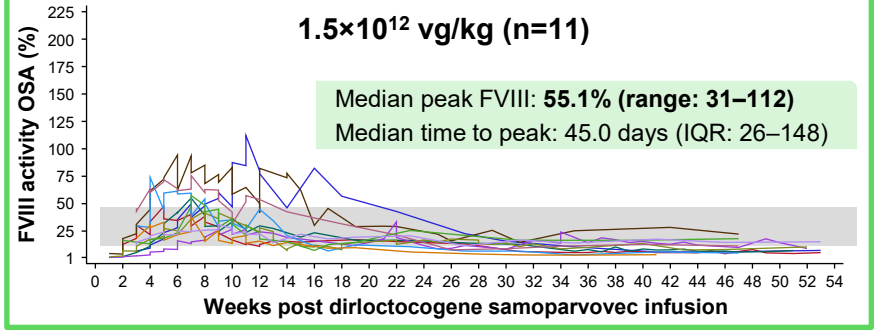
Median time since dosing: 4.6 years (range:1.25–6.5)

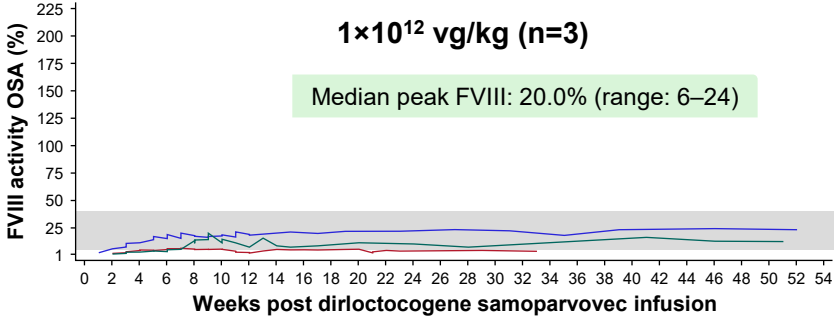


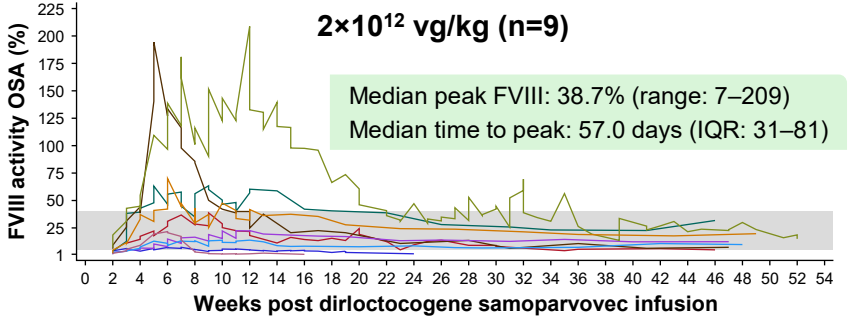
Data cut-off: March 08, 2024. Gray shading indicates the mild HA range. FVIII assessments obtained <5 days after FVIII infusion administration are excluded. F, factor; HA, hemophilia A; OSA, one-stage assay; vg, vector genome

FVIII kinetics show minor, transient peaks in the majority of participants









- Median **time to peak FVIII activity across all participants was 49 days** (range 26–321)
- Transient supraphysiologic (>150%) FVIII activity was seen in only 2/25 participants, both in the 2×10^{12} vg/kg cohort
  - Peak values of 194% and 209% were not sustained or associated with TEs

Gray shading indicates the mild HA range. FVIII assessments obtained <5 days after FVIII infusion are excluded. Median time to peak is not shown for the 5×10^{11} and 1×10^{12} vg/kg dose cohorts since the range of expression has limited variability post infusion. F, factor; IQR, interquartile range; OSA, one-stage assay; TEs, thrombotic events; vg, vector genome

Rapid vector clearance post gene therapy

Time to viral vector DNA clearance

Vector clearance	PBMC (n=22)	Saliva (n=21)	Semen (n=17)	Serum (n=23)	Urine (n=23)
Median, weeks (IQR)	5.5 (4.0–7.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (2.0–3.0)	1.0 (1.0–2.0)
Min, Max, weeks	3, 12	1, 2	1, 3	2, 3	1, 2

- **By 3 weeks**, vector genome concentration was unquantifiable in **saliva, semen, serum, and urine**
- **By 12 weeks**, vector genome concentration was unquantifiable **in PBMCs**

DNA, deoxyribonucleic acid; IQR, interquartile range; PBMCs, peripheral blood mononuclear cells

Conclusions

- These data describe **durable FVIII expression within a narrow range and rapid vector clearance using a low-dose AAV approach**
- Across all dose cohorts, FVIII activity was **sustained within the mild HA range** for most participants
- Peak FVIII expression was within the **normal range** for **dirloctocogene samoparvovec** at the **1.5×10^{12} vg/kg dose** and demonstrated **durable long-term FVIII expression in the range of mild HA**

These PD and previously presented long-term safety and efficacy data[1] support suitability of dirloctocogene samoparvovec as the backbone for an enhanced-function FVIII variant to enable next-generation HA gene therapy

AAV, adeno-associated viral; F, factor; HA, hemophilia A; PD, pharmacodynamics; vg, vector genome

1. George LA, et al. RPTH 2024;8(Suppl. 2):e102503

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Disclosures

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