CR23

Safety and efficacy of gene therapy for hemophilia in HIV-positive participants

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Summary and Conclusions

We describe outcomes in four people with hemophilia A (HA) living with human immunodeficiency virus (HIV) who were treated with dirloctocogene samoparvovec (SPK-8011) or SPK-8016 in Phase I/II trials

Dirloctocogene samoparvovec and SPK-8016 were not associated with additional safety concerns in a subset of participants with HIV and receiving highly active antiretroviral therapy (HAART). Reductions in annualized bleeding rates and annualized factor VIII infusion rates were observed in these participants

The limited data from these four participants suggest carefully selected concomitant HAART is possible for participants receiving liver-directed adeno-associated viral (AAV) vector gene therapies for HA. HIV specialists should be involved in the follow-up of people with HIV when immunomodulation is required

These preliminary results encourage future AAV gene therapy studies that do not exclude people with HA and HIV. Additional clinical investigation is warranted to confirm these findings

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Background

People living with HIV are an important subset within the hemophilia A (HA) community.

Dirloctocogene samoparvovec (SPK-8011) and SPK-8016 are investigational gene therapies for HA that use a modified adeno-associated viral (AAV) vector.

Concerns about the interaction of liver-directed AAV vectors with HIV medications and associated liver damage has led to the exclusion of people with HIV from many gene therapy trials. However, people with HA and living with HIV were not excluded from the Phase I/II trials of dirloctocogene samoparvovec and SPK-8016.

The aim of this analysis is to describe outcomes in four people living with HA and HIV who were treated in Phase I/II trials of dirloctocogene samoparvovec or SPK-8016.

Methods

- Men with HA and living with HIV infection who took part in the Phase I/II SPK-8016-101 (NCT03734588) or SPK-8011-101 (NCT03003533) trials and the long-term follow-up trial (NCT03432520)[1,2] were identified (full study design details are presented in poster CR17).
- Individual safety and efficacy outcomes were assessed in these participants, who were receiving concomitant highly active antiretroviral therapy (HAART) regimens.
- Liver enzyme levels and factor VIII activity levels (determined by one-stage assay) were analyzed by a central laboratory.
- Local laboratories tested participants' levels of tacrolimus (an immunomodulatory therapy that can allow reductions in corticosteroid use) and CD4 count (a blood test that indicates how well the immune system of someone with HIV is functioning).

Results (data cut-off: June 30, 2022)

- Four male participants who were HIV-positive and receiving HAART were included in this analysis (Table 1). Each participant had previously treated hepatitis C virus (HCV) with a negative viral load.
- **Median follow-up:** 3.48 (range: 2.9–4.9) years.

Table 1. Baseline characteristics and medication use

	Dirloctocogene samoparvovec			SPK-8016
	Participant A	Participant B	Participant C	Participant D
Dose cohort	5×10^{11} vg/kg	1×10^{12} vg/kg	1.5×10^{12} vg/kg	5×10^{11} vg/kg
Age (years)	52	48	39	63
Weight (kg)	69.4	88.5	59.8	63.8
Prior factor VIII use*	on demand	on demand	on demand	on demand
HCV treatment history	ledipasvir/sofosbuvir	ledipasvir/sofosbuvir	ledipasvir/sofosbuvir	daclatasvir/sofosbuvir
HAART	emtricitabine, rilpivirine, and tenofovir disoproxil fumarate	abacavir, dolutegravir, and lamivudine	elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide; darunavir†	emtricitabine and tenofovir alafenamide; raltegravir
Immunomodulation after infusion	none	none	prednisolone;‡ tacrolimus	none

*On demand or prophylaxis. †Following elevation of the liver enzyme alanine aminotransferase, HAART regimen was interrupted with the following combinations of agents: [darunavir, cobicistat, emtricitabine and tenofovir alafenamide; dolutegravir]; [emtricitabine and tenofovir alafenamide; darunavir and cobicistat]; and [bictegravir, emtricitabine and tenofovir alafenamide]. ‡Early/prophylactic corticosteroids. HAART, highly active antiretroviral therapy.

One adverse event considered to be related to dirloctocogene samoparvovec was reported; dirloctocogene samoparvovec and SPK-8016 were well tolerated in participants with HIV

8 treatment-related adverse events were reported in **1** participant who received dirloctocogene samoparvovec:

- 1 moderate increase in the liver enzyme alanine aminotransferase (ALT), related to dirloctocogene samoparvovec.
- 7 adverse events related to immunomodulatory therapy: low blood magnesium levels, jitteriness, acne, fluid retention, irritability, osteoporosis (bone weakness), and weight gain.

1 SAE

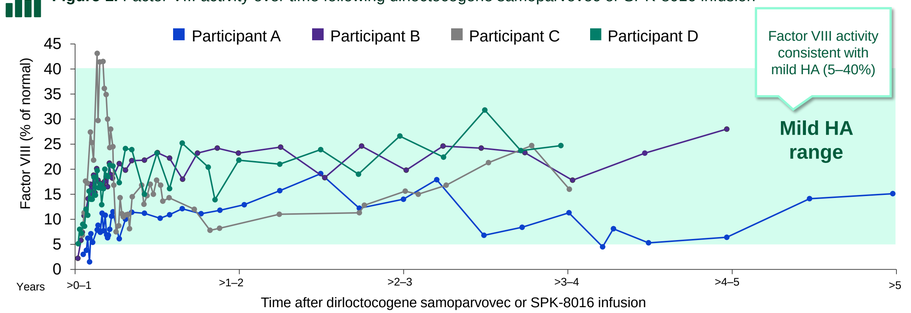
1 serious adverse event (SAE) occurred in the same participant: rhabdomyolysis (muscle breakdown), which was deemed to be unrelated to dirloctocogene samoparvovec.

Three out of four participants with HA and HIV did not require steroid treatment, as a liver immune response was not detected

- In **1** participant, oral corticosteroid therapy was started at Week 2 for a presumed immune response to the AAV vector, in line with a change in protocol requiring prednisolone use by Week 4.
  - Attempts to taper (slowly reduce) the corticosteroid dose were difficult due to intermittent increases in the liver enzyme ALT. Tacrolimus was added to allow reductions in corticosteroid use. The HAART regimen was changed to permit addition of tacrolimus because use of tacrolimus alongside HAART may result in drug–drug interactions.
- The other **3** participants did not require steroid treatment as they did not show signs of a capsid immune response. This may warrant further investigation to establish if a capsid immune response may be less prevalent in those with HIV.

After a follow-up period of 2.9–4.9 years, an infusion of dirloctocogene samoparvovec or SPK-8016 resulted in year-to-year factor VIII expression and reductions in annualized bleeding rate and factor consumption

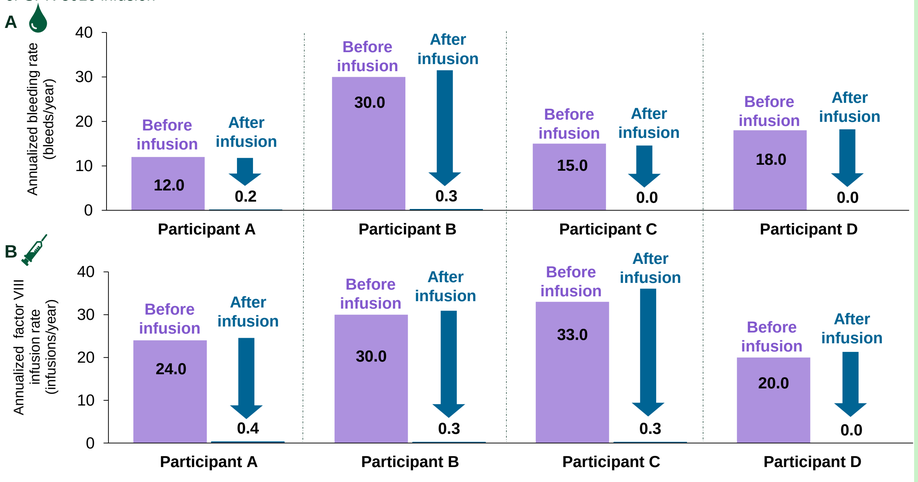
Figure 1. Factor VIII activity over time following dirloctocogene samoparvovec or SPK-8016 infusion



Excludes values within 5 days of factor VIII infusion.

- At the last follow-up for each participant at the data cut-off date, the participants' factor VIII activity was between 15.1–28.0%.

Figure 2. Annualized bleed rate (A) and annualized factor VIII infusion rate (B) before and after dirloctocogene samoparvovec or SPK-8016 infusion



Excludes events in the first 28 days after infusion.

- Annualized bleed rates were reduced by 98.3–100% for all bleeds (Figure 2A), and by 99.2–100% for spontaneous bleeds. Annualized factor VIII infusion rates were reduced by 98.3–100% (Figure 2B).

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References

1. George LA, et al. *N Engl J Med* 2021;385:1961–73.
2. Sullivan S, et al. *Haemophilia* 2021;27(S2):1–192.

Disclosures

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