CR19

Long-Term Follow-Up of Participants in the Phase I/II Trial of Dirloctocogene Samoparvovec (SPK-8011): Durable FVIII Expression and Clinically Meaningful Reduction of Bleeding

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Summary and Conclusions

Updated trial results show that up to 6.5 years post administration of investigational dirloctocogene samoparvovec:

Factor (F)VIII expression was durable and sustained within the mild hemophilia A range for most participants, with near elimination of bleeding and FVIII use (reductions in median annualized bleed rate of 88–99% and annualized FVIII infusion rate of 97–98% compared with historical baseline)

Dirloctocogene samoparvovec was well tolerated; alanine transaminase increases were transient and asymptomatic, and no clinically significant elevations were identified in long-term follow-up

Non-corticosteroid immunoprophylaxis did not prevent corticosteroid use to treat presumed immune response, and intravenous methylprednisolone administration may allow reduced duration of corticosteroid use

Background

Outstanding questions in adeno-associated viral (AAV) gene therapy for hemophilia A (HA) include late transaminase elevations,[1,2] prolonged corticosteroid exposure,[1–4] and uncertainties around durability[1,2,4]

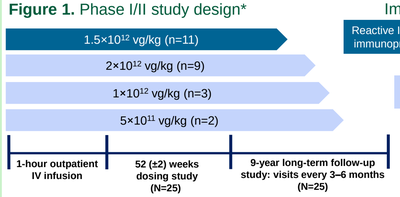
Investigational dirloctocogene samoparvovec gene therapy for HA utilizes doses up to 120× lower than other vectors investigated,[3–6] to minimize dose-dependent toxicities

Previous results from the Phase I/II trial (NCT03003533/NCT03432520) indicated the therapy was well tolerated, with meaningful efficacy and sustained factor (F)VIII activity.[7] Here we present updated results up to 6.5 years post dirloctocogene samoparvovec infusion

Methods

- The primary study objective was to evaluate the safety and efficacy of dirloctocogene samoparvovec
- Multiple immunomodulatory regimens were explored, including steroid-sparing approaches that may allow reduced corticosteroid use (**Figure 1**)
- Eligibility criteria included adult males ≥18 with FVIII activity ≤2%, no history of FVIII inhibitors, and <1:1 neutralizing antibodies to SPK200

Figure 1. Phase I/II study design*



Data cut-off: March 08, 2024. *NCT03003533/NCT03432520; †Tocilizumab and mycophenolate mofetil. IV, intravenous; vg, vector genome

Results

- At data cut-off, 25 participants had received dirloctocogene samoparvovec (**Table 1**). Median time since dosing was 4.6 years (range: 1.25–6.5)
- All 25 participants completed the dosing study and entered long-term follow-up
- There are 21 participants ongoing in follow-up:
  - One participant completed the 4-year follow-up study and declined to enroll in the extension to 9 years
  - Three participants terminated study participation during the follow-up study due to: withdrawal by subject, study-site closure, and lost to follow-up

Table 1. Participant enrollment characteristics

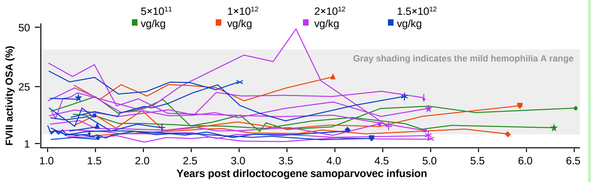
	All participants (N=25)
Median age at informed consent, years (min, max)	34.0 (18, 52)
FVIII severity level at baseline, n (%) <1% ≥1–≤2%	 23 (92.0) 2 (8.0)
Median BMI at baseline, kg/m^2 (min, max)	25.7 (19, 42)
Race, n (%) White Black/African American	 23 (92.0) 2 (8.0)
Prior FVIII treatment, n (%) On demand Prophylaxis	 5 (20.0) 20 (80.0)
Presence of target joints at baseline, n (%) Median number of target joints, n (min, max)	8 (32.0) 2.5 (1, 4)

BMI, body mass index; F, factor

Dirloctocogene samoparvovec resulted in durable and sustained FVIII expression

- There was durable FVIII expression in 20 participants remaining off prophylaxis
- FVIII expression was sustained within the mild HA range in most participants (**Figure 2**)
- Five participants returned to prophylaxis: two lost expression after <1 year due to a presumed capsid immune response, and three had late return to prophylaxis during long-term follow-up with FVIII coagulant activity <5%

Figure 2. FVIII expression post dirloctocogene samoparvovec infusion



Data are censored for the five participants who returned to prophylaxis at the point of their return to prophylaxis. Each line with an associated symbol denotes an individual participant. F, factor; OSA, one-stage assay; vg, vector genome

There were clinically meaningful reductions in annualized bleed rate (ABR) and annualized FVIII infusion rate (AIR)

- The median efficacy follow-up period was 4.3 years (range: 0.2–5.4)
- Overall median ABR (**Figure 3**) was 0.6 (Q1–Q3: 0.0–2.3) for total bleeds, and 0.0 (0.0–0.6) for spontaneous bleeds
- Overall median AIR (**Figure 4**) was 1.2 (Q1–Q3: 0.0–5.1)
- There was 100% target joint resolution in the eight participants with target joints at baseline

Figure 3. Annualized bleeding rate

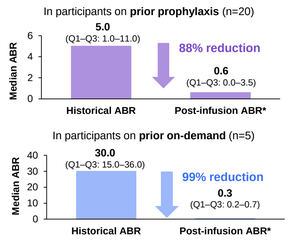
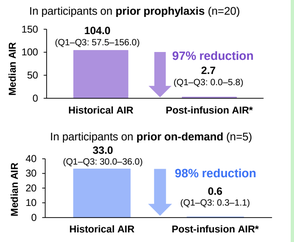


Figure 4. Annualized FVIII infusion rate



*Data exclude first 28 days post infusion. Data are censored for the five participants who returned to prophylaxis at the point of their return to prophylaxis. ABR, annualized bleeding rate; AIR, annualized infusion rate; F, factor; Q, quartile

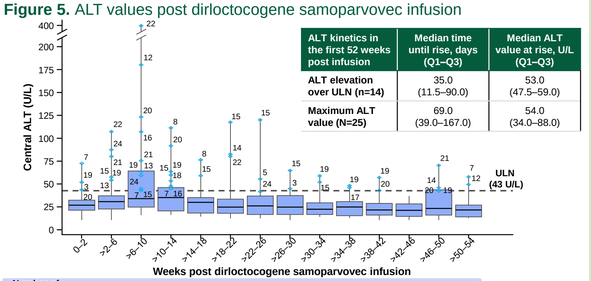
Dirloctocogene samoparvovec was well tolerated

- The median safety follow-up period was 4.6 years (range: 1.25–5.5). In total, 254 adverse events (AEs) occurred
- Five serious AEs (n=5), all resolved:
  - One dirloctocogene-related, a Grade 2 elevation in alanine transaminase (ALT, a liver enzyme)
- No deaths, thrombotic events, or FVIII inhibitor development were reported
- There were 25 dirloctocogene-related AEs (n=14):
  - Most transaminase/ALT elevations, all transient and clinically asymptomatic
    - 10 transaminase elevations (n=7), 4 mild and 6 moderate
    - 11 ALT elevations (n=6), all mild
  - One infusion reaction reported as 4 non-serious events (n=1), all resolved within 24–48 hours

ALT increases were mild and transient, with most within normal range in the first 52 weeks

- Within 1 year, 14 participants had transient ALT elevation exceeding upper limit of normal (**Figure 5**). Median time until rise was 35 days (Q1–Q3: 11.5–90)

Figure 5. ALT values post dirloctocogene samoparvovec infusion



ALT kinetics in the first 52 weeks post infusion	Median time until rise, days (Q1–Q3)	Median ALT value at rise, U/L (Q1–Q3)
ALT elevation over ULN (n=14)	35.0 (11.5–90.0)	53.0 (47.5–59.0)
Maximum ALT value (N=25)	69.0 (39.0–167.0)	54.0 (34.0–88.0)

Maximum ALT value per person is plotted in each time period. Boxes represent IQR; lines inside boxes are medians. Vertical lines represent range. Diamonds indicate values above ULN with the participant number. ALT, alanine transaminase; IQR, interquartile range; Q, quartile; U/L, units per liter; ULN, upper limit of normal

- Isolated single ALT elevations (above upper limit of normal and resolved at next assessment) were observed in long-term follow-up:
  - All were Grade 1, none reported as AEs or deemed clinically significant; five participants (20%) had such elevations in Year 2, and five (20%) beyond Year 2

Non-corticosteroid immunoprophylaxis did not prevent corticosteroid use to treat presumed immune response, but IV methylprednisolone may allow reduced duration of corticosteroids

- Data on oral corticosteroid administration in the first three dosing cohorts have been previously presented[8]
- In the 1.5×10^{12} vg/kg dose cohort (n=11), steroid and steroid-sparing approaches were explored (**Table 2**); 7 participants received non-corticosteroid immunoprophylaxis of tocilizumab (n=4) or mycophenolate mofetil (n=3)
  - Six of these participants required subsequent corticosteroid intervention

Table 2. Immunomodulation received in the 1.5×10^{12} vg/kg cohort (n=11)

	Planned immunomodulation regimen		
	Corticosteroid (n=4)	Tocilizumab (n=4)	MMF (n=3)
No corticosteroids, n	0	0	1
Corticosteroids, n			
Oral	3	1	0
IV methylprednisolone	1	3	2

IV, intravenous; MMF, mycophenolate mofetil; vg, vector genome

- Duration of corticosteroid exposure was shorter in participants receiving IV methylprednisolone compared with oral corticosteroids only:
  - IV methylprednisolone: median 31 days, range: 8–88 days
  - Oral corticosteroids: median 110 days, range: 53–306 days

There were no new immunomodulation-related safety signals

- There were 36 immunomodulation-related AEs (n=9):
  - 25 (n=6) were related to corticosteroids
  - 11 (n=6) were related to non-corticosteroid immunoprophylaxis
- Most common AEs were insomnia, weight gain, and fatigue (four events each), and low white blood cell count (three events)
- All AEs resolved, and none were reported as serious
- There were four moderate immunomodulation-related AEs (the rest were mild):
  - These were insomnia (oral corticosteroid), two cases of low white blood cell count (tocilizumab) and acid reflux (IV methylprednisolone)
- None of the immunomodulatory regimens were associated with reports of immunomodulation-related infections

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