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Four-Year Follow-up of the Alta Study, a Phase 1/2 Study of Giroctocogene Fitelparvovec (PF-07055480/SB-525) Gene Therapy in Adults With Severe Hemophilia A

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*At the time of the study

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Hemophilia A

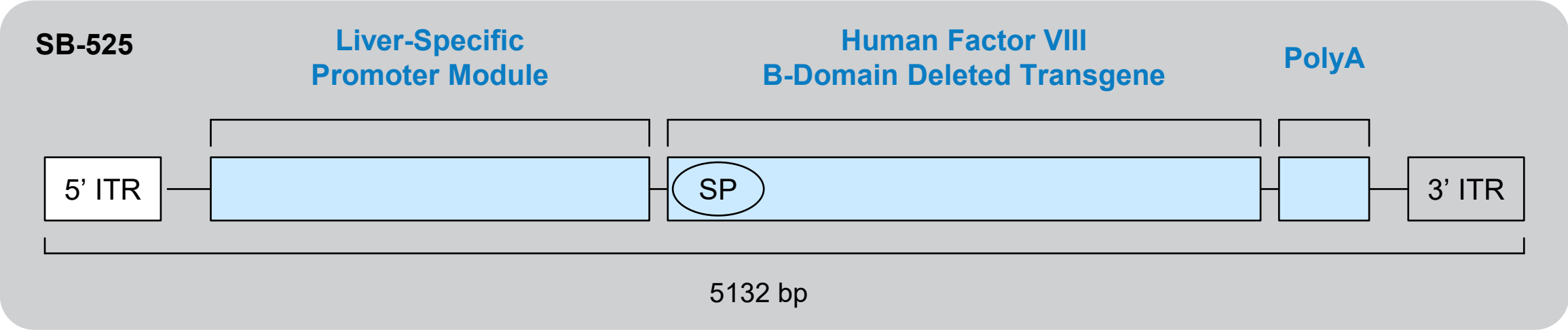
- A rare bleeding disorder caused by pathogenic variants in the *F8* gene, resulting in insufficient FVIII activity
- Current treatment involves replacement therapy with exogenous FVIII or with emerging mimetic-based bispecific antibody therapy, both requiring frequent dosing via IV or SC administration[1]
- Maintenance of FVIII activity in the mild (>5% to <40%) to normal (>50%) range improves outcomes for patients with severe hemophilia A[2]
- Hemophilia A has a wide therapeutic window and a single underlying gene defect, making it an ideal candidate for gene therapy[3]

FVIII=factor VIII; IV=intravenous; SC=subcutaneous

1. Srivastava A, et al. Haemophilia 2020;26(suppl 6):1-158. **2.** White GC, et al. Thromb Haemost 2001;85:560. **3.** Leebeek FWG, et al. Blood 2021;138:923-931.

Giroctocogene fitelparvovec gene therapy for hemophilia A

- AAV-vector–mediated gene transfer enables the delivery of a modified functional *F8* coding sequence to hepatocytes that subsequently synthesize FVIII at levels that may prevent bleeding events in the absence of exogenous FVIII
- Giroctocogene fitelparvovec (formerly SB-525 or PF-07055480) is a liver-tropic rAAV6 vector carrying a B-domain–deleted *F8* gene that is delivered through a single IV infusion



AAV=adeno-associated virus; bp=base pairs; FVII=factor VIII; ITR=inverted terminal repeat; IV=intravenous; rAAV6=recombinant adeno-associated virus serotype 6; SP=signal peptide

Alta: Study population and design

- Phase 1/2, single-dose, multicenter, dose-ranging study to assess the safety and tolerability of giroctocogene fitelparvovec in adults (aged ≥18 years) with severe hemophilia A

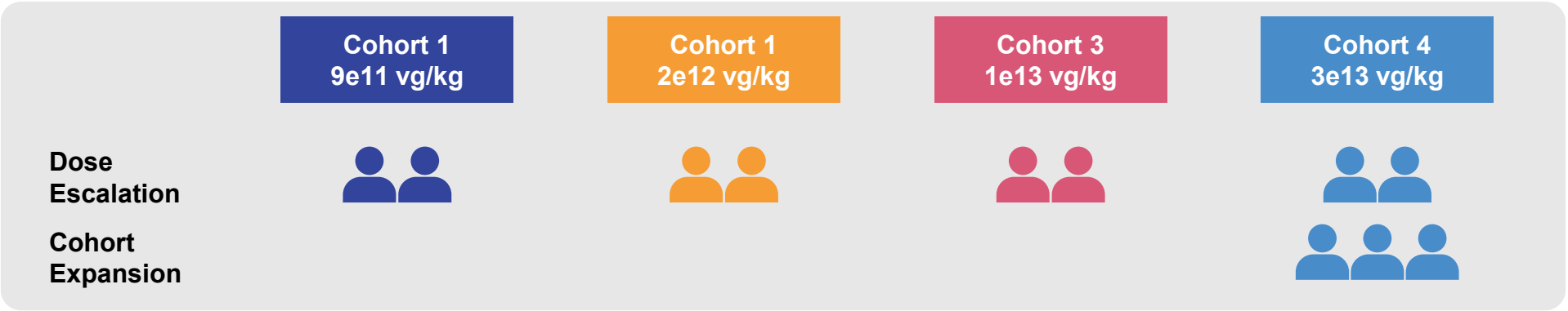
Key Exclusion Criteria

- Neutralizing activity to AAV6 capsid and/or inhibitor to FVIII
- History of hypersensitivity response to FVIII replacement therapy
- History of liver dysfunction
- Contraindication to steroids

Participant Time in Study: 62 months

Screening ~8–10 weeks

Safety/Efficiency evaluation ~60 months (every 6 months after 1st year)



AAV6=adeno-associated virus serotype 6; FVIII=factor VIII

Alta: Endpoints

Primary Endpoints

- Incidence of AEs and SAEs
- Change in circulating FVIII activity

Secondary Endpoints

- Change from baseline in the use of FVIII replacement therapy
- Change in frequency and severity of bleeding episodes
- Measurement of FVIII inhibitor levels
- Vector shedding in bodily fluids

AE=adverse event; FVIII=factor VIII; SAE=serious adverse event

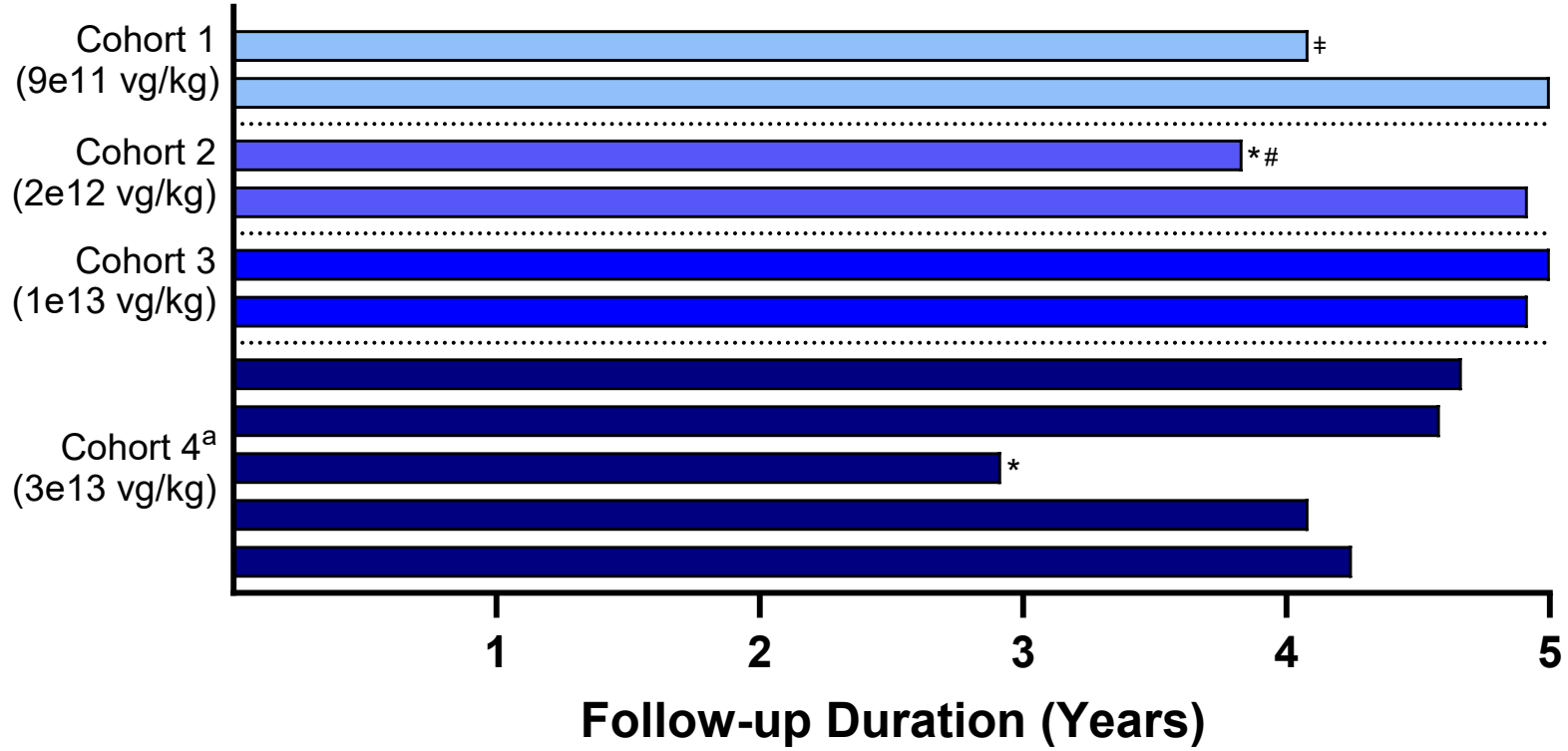
Alta: Participant demographic characteristics

Characteristic		Cohort 1 9e11 vg/kg n=2	Cohort 2 2e12 vg/kg n=2	Cohort 3 1e13 vg/kg n=2	Cohort 4 3e13 vg/kg n=5	All Participants N=11
Age, years	Mean (SD)	30.5 (9.2)	35.5 (16.3)	32.0 (1.4)	26.8 (6.3)	30.0 (7.9)
	Median	30.5	35.5	32.0	29.0	30.0
	Min, max	24, 37	24, 47	31, 33	18, 34	18, 47
Sex, n (%)	Male	2 (100)	2 (100)	2 (100)	5 (100)	11 (100)
Race, n (%)	Asian	–	1 (50)	–	–	1 (9)
	White	2 (100)	1 (50)	2 (100)	4 (80)	9 (82)
	Other	–	–	–	1 (20)	1 (9)
Ethnicity, n (%)	Hispanic or Latino	–	–	–	2 (40)	2 (18)
	Not Hispanic or Latino	2 (100)	2 (100)	2 (100)	3 (60)	9 (82)

Data cut: 08SEP2023

Max=maximum; min=minimum; vg=vector genomes

Alta: Follow-up duration



11 participants were dosed, all completed 3 years (156 weeks) follow-up
4 completed 5 years, 5 completed 4 years, 2 left the study after 3 years, 1 was lost to follow-up (in Year 5)

‡ Participant lost to follow-up.

* Participants did not consent to continued follow-up after Year 3 (Week 156). # Participant terminated study earlier (at Year 4).

[a] In Cohort 4, 2/5 participants completed 4.5 years (Week 234), 2 completed 4 years (Week 208), 1 left the study after 3 years (Week 156). Vg=vector genomes.

Alta: Treatment-related adverse events

MedDRA Preferred Term	Cohort 2 2e12 vg/kg n=2		Cohort 4 3e13 vg/kg n=5		All Participants N=11	
	n (%)	No. of Events	n (%)	No. of Events	n	No. of Events
Any treatment-related event	2 (100)	5	4 (80)	22	6 (55)	27
Grade 3/4 AE	0	0	1 (20)[a]	1	1 (9)	1
ALT increased[b]	2 (100)	3	3 (60)	10	5 (46)	13
AST increased[b]	1 (50)	2	2 (40)	3	3 (27)	5
Pyrexia[b]	0	0	3 (60)	3	3 (27)	3
Tachycardia[b]	0	0	2 (40)	2	2 (18)	2
Myalgia	0	0	1 (20)	1	1 (9)	1
Hypotension[b]	0	0	1 (20)	1	1 (9)	1
Fatigue	0	0	1 (20)	1	1 (9)	1
FVIII level increased[b]	0	0	1 (20)	1	1 (9)	1

- No treatment-related AEs reported for participants in Cohorts 1 and 3
- Infusion-related reactions, occurring within a day of dosing, were reported in 4 of 5 participants in Cohort 4
  - Tachycardia (grade 1, n=2), pyrexia (grades 1 and 2, n=3), and hypotension (grade 3, n=1)

[a] One participant experienced grade 3 hypotension and grade 2 fever that was an SAE considered related to study drug and resolved with treatment within 24 h.

[b] Denotes AE of special interest.

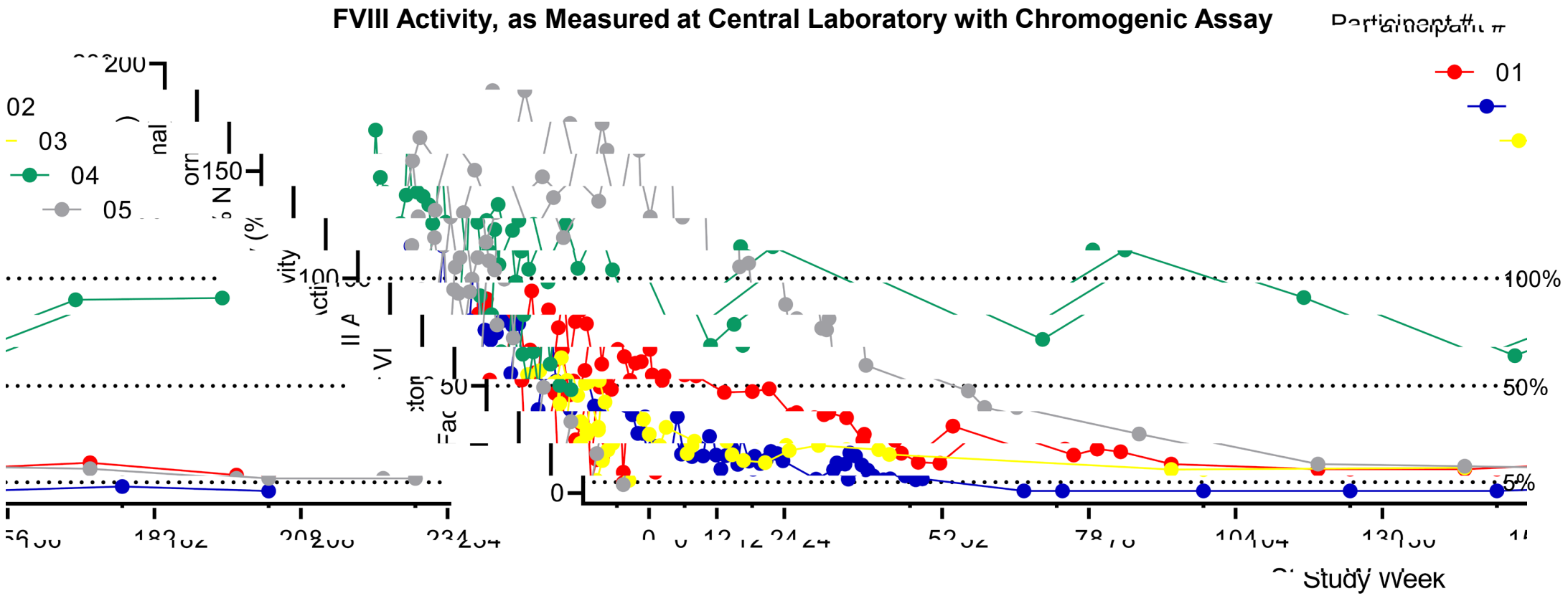
AE=adverse event; ALT=alanine transaminase; AST=aspartate aminotransferase; SAE=serious adverse event; vg=vector genomes

Alta: Safety summary

- A total of 116 treatment-emergent AEs (all causalities) occurred in 11 participants
- 27 treatment-related AEs occurred in 6 participants; the most common were:
  - ALT increase: 13 events in 5 participants (Cohorts 2 and 4)
  - AST increase: 5 events in 3 participants (Cohorts 2 and 4)
- 4 of 5 participants in Cohort 4 required >7 days of corticosteroid treatment for ALT/AST elevations (by laboratory criteria); all resolved with intervention
  - LFT elevations were managed with tapering corticosteroids (median: 56 days; range: 7–135 days)
  - No Cohort 4 participants have required steroids since Week 65; all continue to have ALT values in the normal range (follow-up range: 156–234 weeks) and normal findings via liver MRI (follow-up range: 104–208 weeks)
- 1 participant in Cohort 4 experienced treatment-related SAEs of grade 3 hypotension and grade 2 fever ~6 h after completion of the vector infusion, the events fully resolved with treatment
- No confirmed FVIII inhibitor development occurred
- No thrombotic events, neoplastic events, abnormal AFP, and/or liver masses were reported

AE=adverse event; AFP=alfa-fetoprotein; ALT=alanine transaminase; AST=aspartate aminotransferase; FVIII=factor VIII; LFT=liver function test; SAE=serious adverse event

Alta: FVIII activity (Cohort 4 participants)



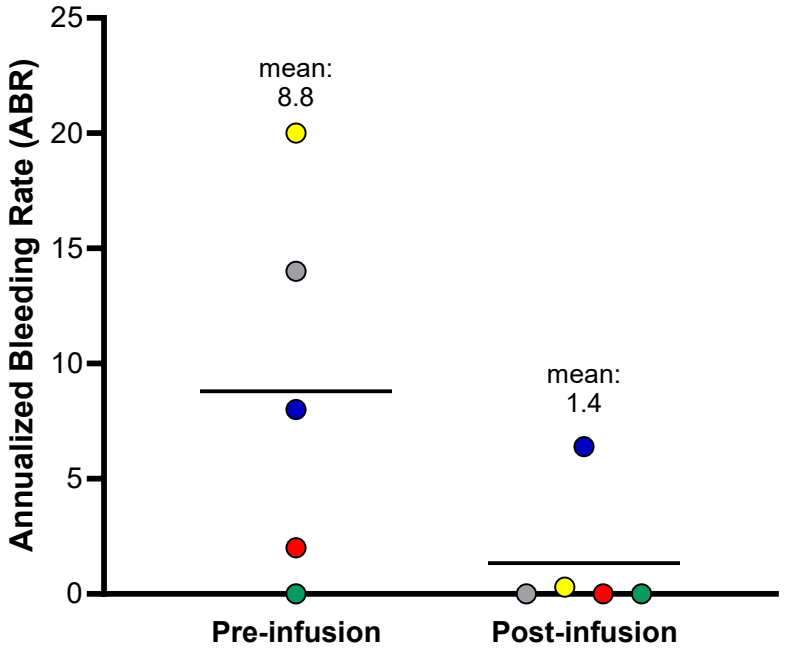
Study Week	Week 78 n=4	Week 104 n=5	Week 130 n=4	Week 156 n=5	Week 182 n=4	Week 208 n=4
Median, Mean, %	40.1, 49.0	16.3, 25.4	12.3, 34.7	11.8, 25.5	12.7, 23.1	7.6, 26.6

Mild range: >5% to <40%; normal range: >50%.

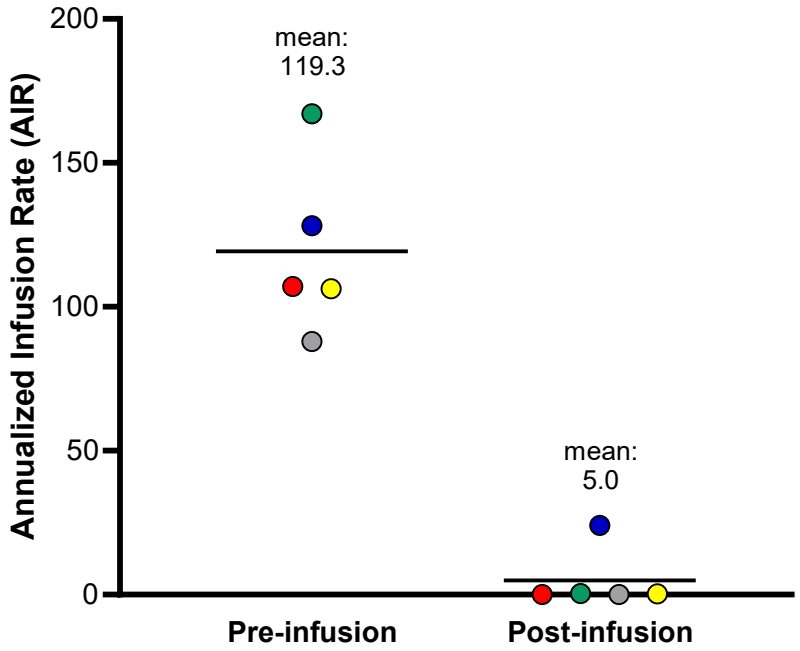
Latest available FVIII values from September 2023 data cut.

FVIII=factor VIII.

Alta: ABR and AIR (Cohort 4 participants)



Post-infusion:
Mean overall ABR = 1.4
Median overall ABR = 0.0



Post-infusion:
Mean overall AIR = 5.0
Median overall AIR = 0.4

ABR calculated as: (number of all bleeding episodes starting 3 weeks after study drug infusion)/(observation period in years).
AIR calculated as: (number of FVIII replacement therapy infusions starting 3 weeks after study drug infusion)/(observation period in years).
ABR=annualized bleeding rate; AIR=annualized infusion rate.

Alta: Bleeding events (Cohort 4)

- 0 bleeding events occurred in the first year post infusion
- Median and mean (SD) ABR = 0.0 and 1.4 (2.82) for total duration of follow-up (n=5 participants with ≥3 years of follow-up)
- 3 of 5 participants (60%) experienced no bleeds
- 2 participants experienced bleeding events necessitating treatment with exogenous FVIII; all bleeding events occurred after Week 67 post infusion
  - 25 treated bleeding events in 1 participant (#02): 11 traumatic, 8 spontaneous, 6 unknown
  - 1 bleeding event in a target joint in 1 participant (#03): circumstances unknown
- Maintenance of FVIII activity (measured with chromogenic assay)
  - 2 participants with 4.5-year follow-up: mild (6.8%) to normal (90.9%) range
  - 2 participants with 4-year follow-up: 1 in mild range (8.4%); 1 with FVIII activity BLOQ
  - 1 participant left study after 3 years follow-up: mild range (11.8%)
- No participants in Cohort 4 have resumed prophylaxis

ABR calculated as: (number of all bleeding episodes starting 3 weeks after study drug infusion)/(observation period in years).

ABR=annualized bleeding rate; BLOQ=below limit of quantification; FVIII=factor VIII

Conclusions

- A single infusion of giroctocogene fitelparvovec gene therapy in participants with severe hemophilia A was generally well tolerated, with associated increases in FVIII levels, transient AEs, and mean ABR of 1.4 in the highest-dose cohort (3e13 vg/kg)
- Additional follow-up is required to assess durability of efficacy and other long-term effects of giroctocogene fitelparvovec, such as impact on overall liver health
- A phase 3 study (NCT04370054) of giroctocogene fitelparvovec in participants with hemophilia A is ongoing and will provide more long-term data on safety and durability

ABR=annualized bleeding event; AE=adverse event; FVIII=factor VIII; vg=vector genomes

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