

Update for the Alta Study, a Phase 1/2 Gene Therapy Trial of Giroctocogene Fitelparvovec (SB-525) in Adults With Severe Hemophilia A

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Presented at the American Society of Hematology Annual Meeting, December 2–11, 2020, virtual event

Disclosures for: Andrew D. Leavitt, MD

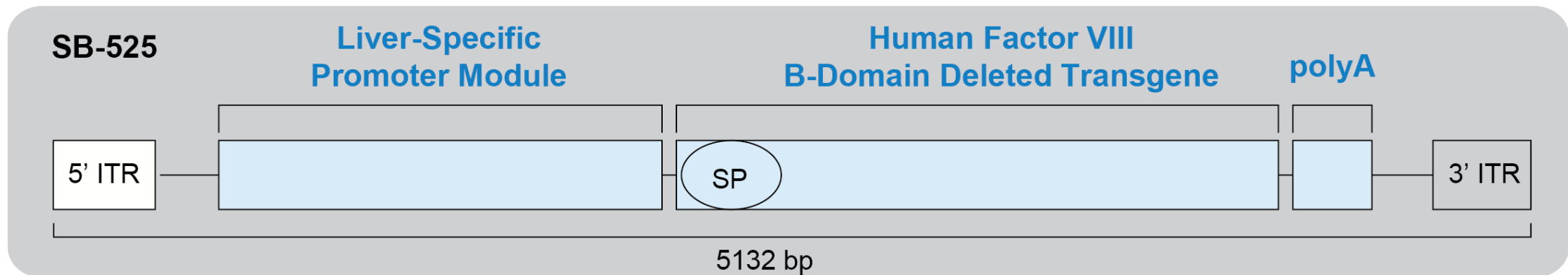
Conflict	Disclosure
Research Support	None
Director, Officer, Employee	None
Shareholder	Johnson & Johnson
Honoraria	None
Advisory Committee	BioMarin; Dova Pharmaceuticals; Catalyst Biosciences; Bio Products Laboratory
Consultant	Merck

Hemophilia A

- A bleeding disorder due to low circulating factor VIII (FVIII) activity levels secondary to *F8* gene mutations
 - Current treatment involves replacement therapy with exogenous FVIII, or with emerging mimetic-based therapy
 - Current treatment require frequent dosing via intravenous (IV) or subcutaneous administration
 - Maintenance of FVIII activity in the mild (>5%) to normal range improves outcomes for patients with severe hemophilia A
 - The wide therapeutic window and underlying single gene defect make hemophilia A an ideal candidate for gene therapy
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Giroctocogene Fitelparvovec Gene Therapy for Hemophilia A

- 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

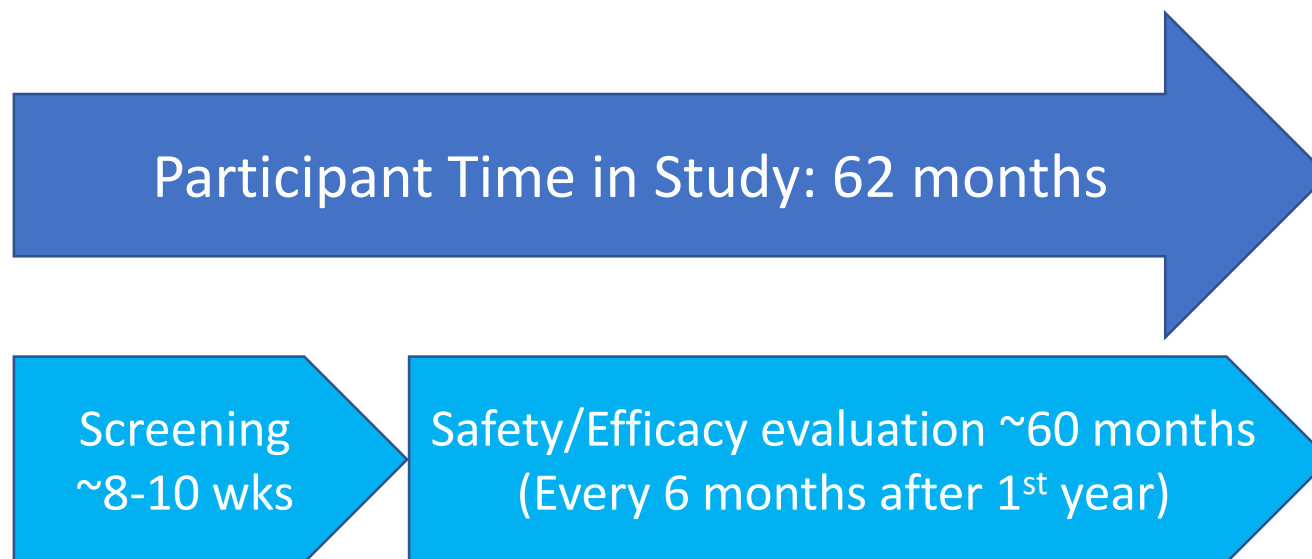


Alta Study Design

- Alta is a phase 1/2, dose-ranging, single-dose, multicenter study to assess the safety and tolerability of giroctocogene fitelparvovec in adult participants (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

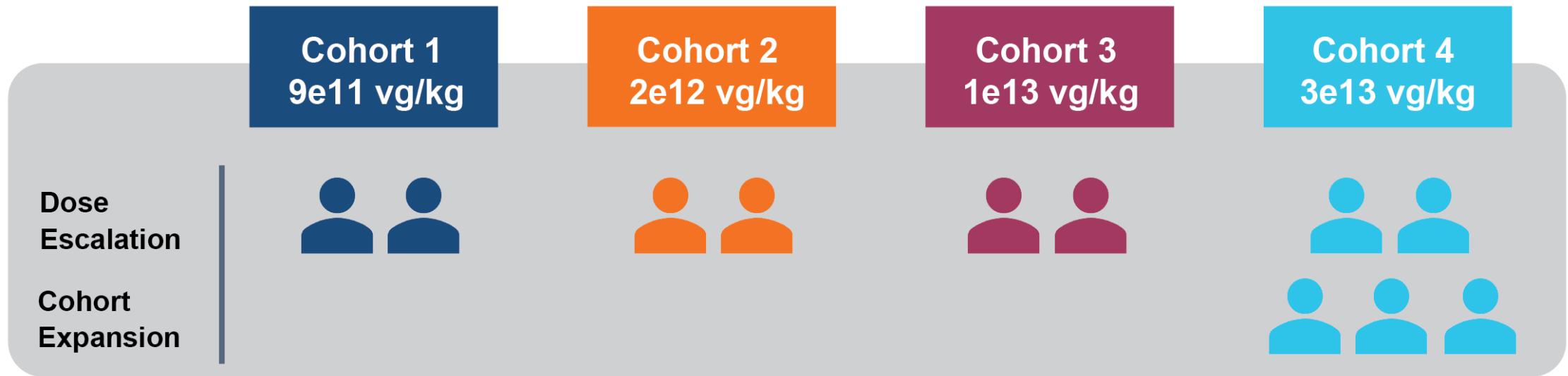


Study End Points

- Primary end points
 - Incidence of AEs and SAEs
 - Change in circulating FVIII activity
- Secondary end points
 - Change from baseline for FVIII replacement therapy
 - Change in frequency and severity of bleeding episodes
 - Measurement of FVIII inhibitor levels
 - Vector shedding in bodily fluids

Study Design

- 4 dose cohorts, 2 participants each, and a high-dose cohort expansion of 3 participants (total of 11 participants dosed) with reactive corticosteroid use
- Corticosteroid treatment is initiated for ALT elevation that exceeds 1.5x baseline value
- Safety and efficacy data of each cohort were reviewed by an independent safety monitoring committee prior to each dose escalation and prior to initiating cohort 4 expansion
- Follow-up duration ranges from 1 to 3 years post infusion except for 1 participant in the 1e13-vg/kg cohort who prematurely discontinued the study (lost to follow-up)



Participant Demographics

Characteristic		Cohort 1 9e11 vg/kg	Cohort 2 2e12 vg/kg	Cohort 3 1e13 vg/kg	Cohort 4 3e13 vg/kg	All Participants
Age, years	n	2	2	2	5	11
	Mean (SD)	30.5 (9.19)	35.5 (16.26)	32.5 (0.71)	27.2 (6.10)	30.3 (7.81)
	Median	30.5	35.5	32.5	29.0	31.0
	Min, max	24, 37	24, 47	32, 33	19, 34	19, 47
Sex, n (%)	Male	2 (100)	2 (100)	2 (100)	5 (100)	11 (100)
Race, n (%)	Asian	–	1 (50)	–	–	1 (9.1)
	White	2 (100)	1 (50)	2 (100)	4 (80.0)	9 (81.8)
	Other	–	–	–	1 (20.0)	1 (9.1)
Ethnicity, n (%)	Hispanic or Latino	–	–	–	2 (40.0)	2 (18.2)
	Not Hispanic or Latino	2 (100)	2 (100)	2 (100)	3 (60.0)	9 (81.8)

Max, maximum; min, minimum; SD, standard deviation; vg, vector genomes.
Data cut: 31 August 2020.

Safety Summary

- 26 treatment-related AEs occurred in 6 participants, with most common being:
 - ALT: 13^a events in 5 participants (cohorts 2 and 4)
 - AST: 5 events in 3 participants (cohorts 2 and 4)
- 1 participant in cohort 4 (3e13 vg/kg) experienced treatment-related SAEs of grade 3 hypotension and grade 2 fever along with headache and tachycardia ≈6 hours after completion of the vector infusion and resolved ≈12 hours post infusion
- No participant experienced a COVID-19 related AE
- No participant developed FVIII inhibitors
- 4 of 5 participants in cohort 4 required corticosteroid treatment for liver transaminase (ALT/AST) elevation; all resolved with intervention
 - 3 of the 4 had subsequent transaminase elevation after resolution of the initial increase, 1 of the 3 had an additional elevation; all transaminase elevations resolved with corticosteroids.
- No initiation of corticosteroid use was required to date after week 52 and all participants are currently off corticosteroids.

^aOne participant had an ALT increase per central lab results, but Investigator has not reported increase as an adverse event.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FVIII, factor VIII; SAE, serious adverse event; vg, vector genomes.

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)	
	Subjects, n (%)	No. of Events	Subjects, n (%)	No. of Events	Subjects, n (%)	No. of Events
Any treatment-related event	2 (100.0)	5	4 (80.0)	21	6 (54.4)	26
ALT increased ^a	2 (100.0)	3	3 (60.0)	10	5 (45.5)	13
Pyrexia			3 (60.0)	3	3 (27.3)	3
AST increased	1 (50.0)	2	2 (40.0)	3	3 (27.3)	5
Tachycardia			2 (40.0)	2	2 (18.2)	2
Fatigue			1 (20.0)	1	1 (9.1)	1
Hypotension			1 (20.0)	1	1 (9.1)	1
Myalgia			1 (20.0)	1	1 (9.1)	1

- No treatment-related AEs for participants in cohorts 1 and 3

^aOne participant had an ALT increase per central lab results that the Investigator has not reported increase as an adverse event.
Data cut: 31 August 2020. AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; vg, vector genomes.

ALT Elevations: Cohort 4 (3 x 10¹³ vg/kg)

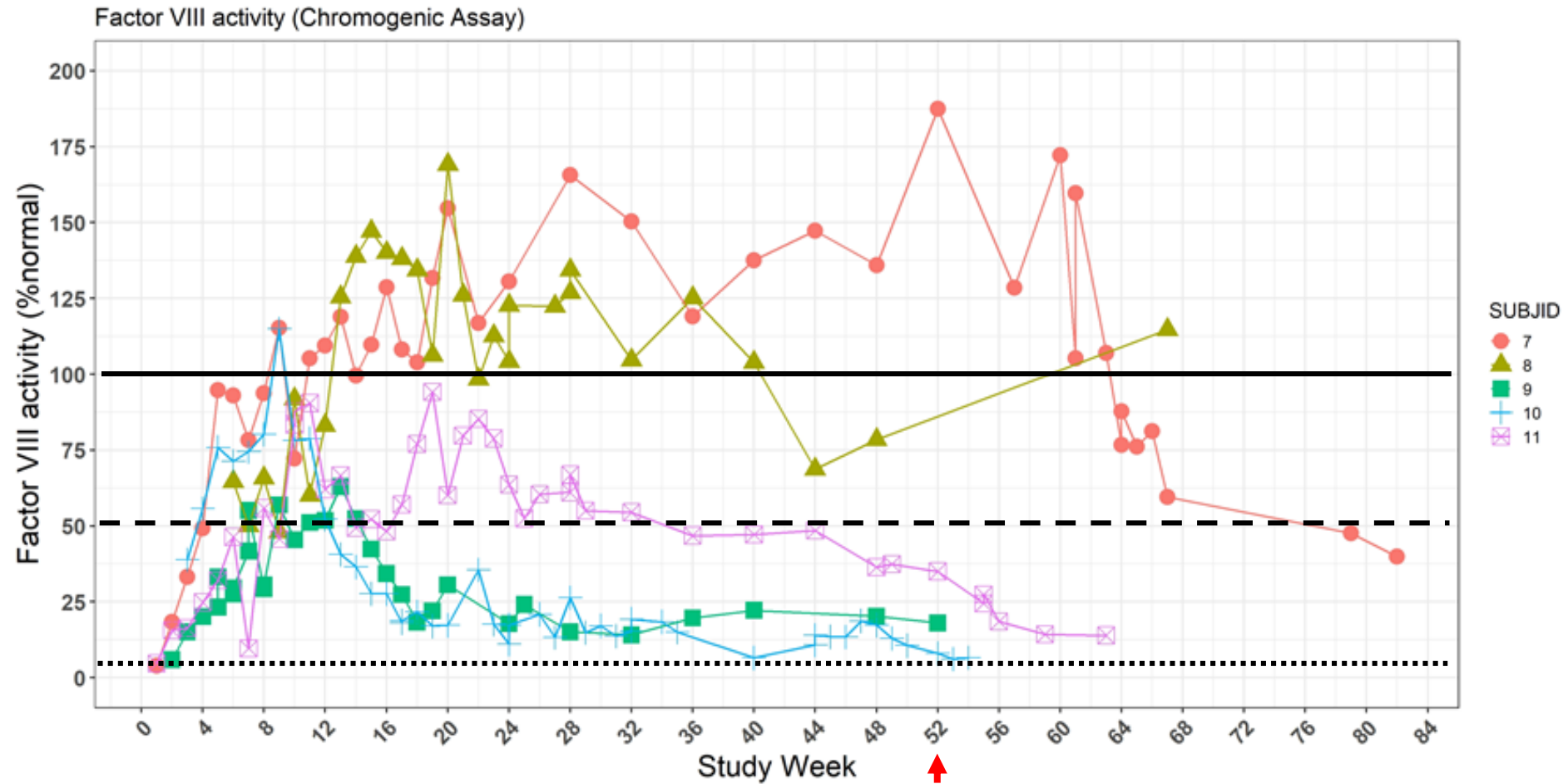
- 4 of 5 participants in cohort 4 had an ALT elevation

Participant ID Number	Time of First ALT Elevation (Week)	Maximum ALT Value, U/L (Grade)	Corticosteroid Treatment Duration (Weeks)	FVIII Levels (Chromo, IU/dL) at Start of Corticosteroids	FVIII Levels (Chromo, IU/dL) at End of Taper	Time of Second ALT Elevation (Week)	Weeks of Corticosteroids After Second Elevation
7	4.5	91 (gr 1)	11	94.8	108.2	48 ^a	16 ^a
8	12	66 (gr 1)	16	83.1	112.6	N/A	N/A
10	5.5	91 (gr 1)	6	46.4	57.1	20	9
11	8	192 (gr 2)	7	80.2	27.7	16	18

^aParticipant had an additional isolated elevation of ALT at week 28 that was treated with corticosteroids for 1 week, then discontinued (not reported as AE). Data cut: 31 August 2020. ALT, alanine transaminase; chromo, chromogenic assay; FVIII, factor VIII; N/A, not available; vg, vector genomes.

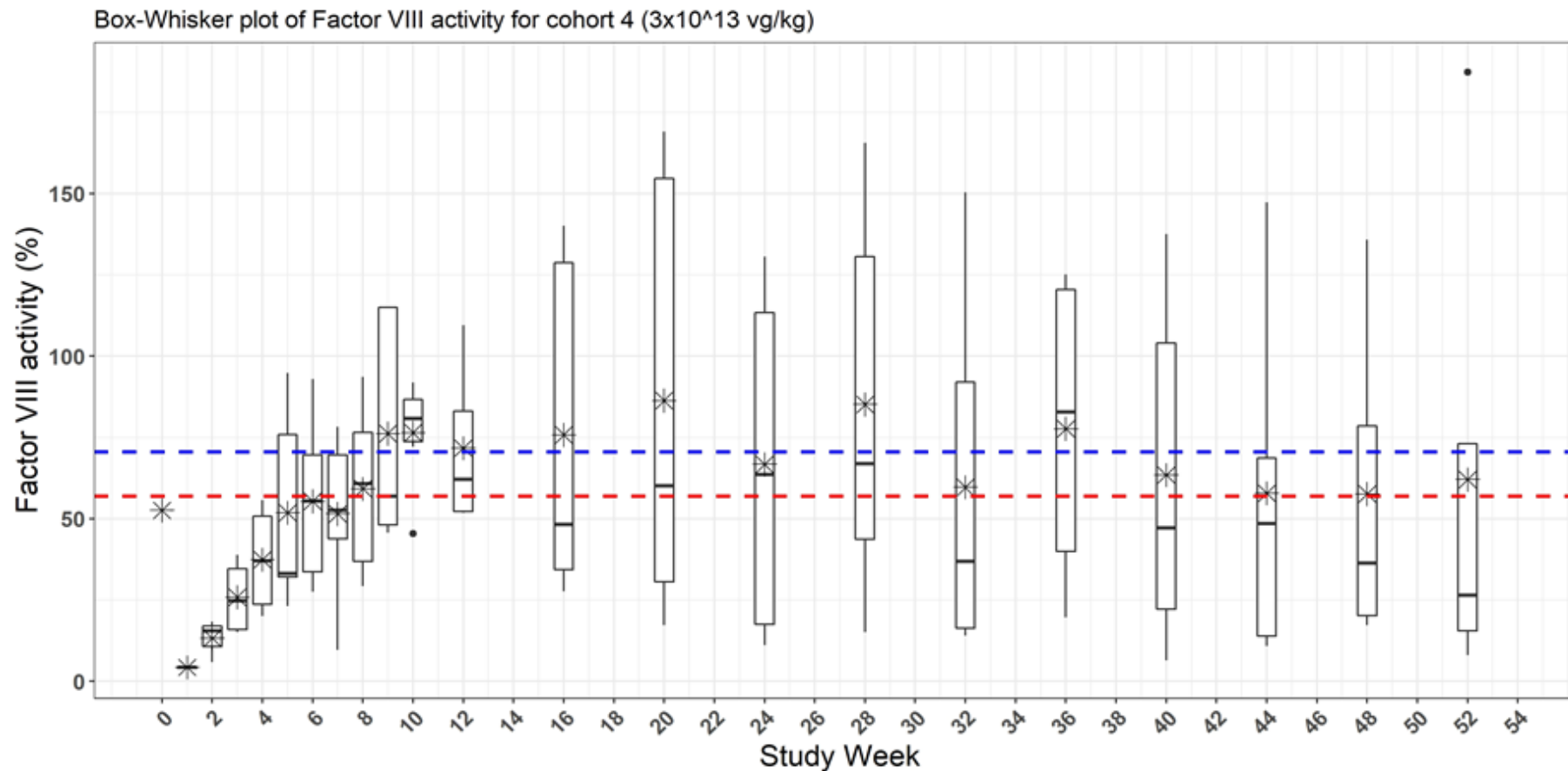
Efficacy – Cohort 4 (3e13 vg/kg)

FVIII Activity as Measured at Central Laboratory With Chromogenic Assay



Latest available FVIII values from August 2020 data cut.
FVIII, factor VIII; vg, vector genomes.

Efficacy – Central Laboratory, Chromogenic Assay



- - - Mean FVIII activity from week 9 to week 52 (based on group mean): 70.4% (SD=7.3%)
- - - Median FVIII activity from week 9 to week 52 (based on group median): 56.9% (SD=14.2%)
- * Mean (box and whisker plot)
- Median (box and whisker plot)
- Outliers

Week 52: n=4 participants
1 participant had FVIII measured at week 67 instead of week 52 due to COVID-19 restrictions

Data cut: 31 August 2020.

FVIII, factor VIII; vg, vector genomes; SD, standard deviation.

Efficacy Summary

- FVIII activity increase from baseline was generally dose dependent
- At 24 months, 1 participant in Cohort 3 remains in the mild range for factor VIII activity
- **Cohort 4 (3e13 vg/kg)**
 - Steady-state FVIII activity achieved by week 9 post infusion
 - Median steady-state (of geometric means from week 9 to latest follow up) FVIII activity level 50.2% (mean 63%) via central laboratory chromogenic assay (includes all FVIII levels up to data cut)
 - One treated target joint bleed was reported during the 2nd year following vector infusion.

Conclusions

- Interim data with at least 1 year and up to 3 years of follow up post infusion continue to show that giroctocogene fitelparvovec is generally well tolerated
 - 1 participant experienced treatment-related SAE immediately following vector infusion, no additional treatment-related SAE
- Cohort 4 (3e13 vg/kg) Participants achieved steady state at week 9, with mean FVIII activity maintained through week 52
- The ongoing phase 1/2 study supports further development of giroctocogene fitelparvovec

Development Update: First participant in the AFFINE phase 3 study (3e13 vg/kg) was dosed in October 2020

Acknowledgments

The investigators acknowledge and thank all study participants.

We also acknowledge and thank Pfizer Study Clinicians Delphine Agathon and Anne Yver for their work on this presentation and this study, as well as the site staff, and Sangamo and Pfizer Study Teams for their contributions and conduct of the trial.