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

Nathan Visweshwar, MD[1]; Thomas J. Harrington, MD[2]; Andrew D. Leavitt, MD[3]; Barbara A. Konkle, MD[4]; Adam Giermasz, MD, PhD[5]; Kimo C. Stine, MD[6]; Jeremy Rupon, MD, PhD[7]; Gregory Di Russo, MD[7]; Li-Jung Tseng, PhD, MBA[8]; Maria de los Angeles Resa, PhD[8]; Florence Ganne, PhD[9]; Delphine Agathon, PhD[9]; Frank Plonski, RN, MA[7]; Didier Rouy, MD, PhD[10]; Bettina M. Cockroft, MD, MBA[10]; Annie Fang, MD, PhD[8]; Steven Arkin, MD[11]

[1]University of South Florida, Tampa, FL; [2]University of Miami Miller School of Medicine, Miami, FL; [3]University of California, San Francisco, San Francisco, CA; [4]Bloodworks Northwest and the University of Washington, Seattle, WA; [5]University of California Davis, Sacramento, CA; [6]UAMS at Arkansas Children's Hospital, Little Rock, AR; [7]Pfizer Inc., Collegeville, PA; [8]Pfizer Inc., New York, NY; [9]Pfizer Inc., Paris, France; [10]Sangamo Therapeutics, Brisbane, CA; [11]Pfizer Inc., Cambridge, MA

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Disclosures for Nathan Visweshwar

Conflict	Disclosure
Advisory board	Biogen Idec

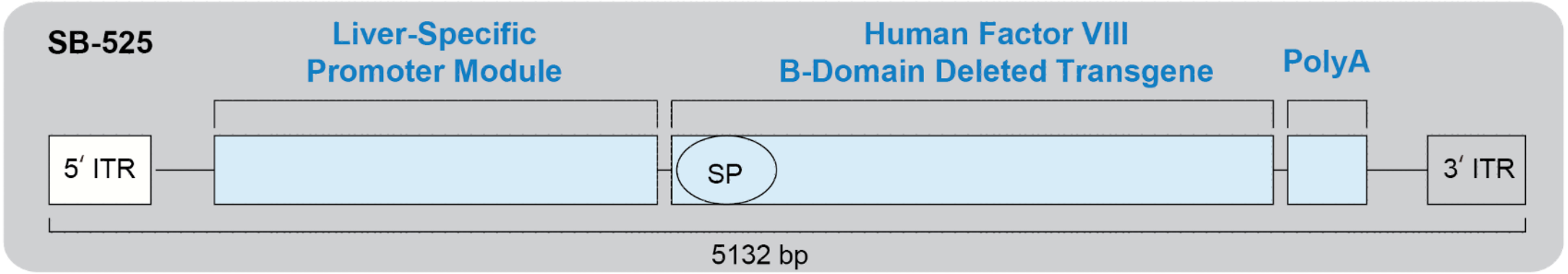
Hemophilia A

- 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
- Maintenance of FVIII activity in the mild (>5% to <40%) to normal (>50%) range improves outcomes for patients with severe hemophilia A
- Hemophilia A has a wide therapeutic window and a single underlying gene defect, making it an ideal candidate for gene therapy

FVIII, factor VIII; IV, intravenous; SC, subcutaneous.

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, internal tandem repeat; IV, intravenous; rAAV6, recombinant adeno-associated virus serotype 6; SP, signal peptide.

Alta Study 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
- Liver dysfunction
- Contraindication to steroids

Participant time in study: 62 months

Screening ≈8–10 wks

Safety/efficacy evaluation ≈60 months (every 6 months after 1st year)

AAV6, adeno-associated virus serotype 6; FVIII, factor VIII.

Study End Points

PRIMARY END POINTS

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

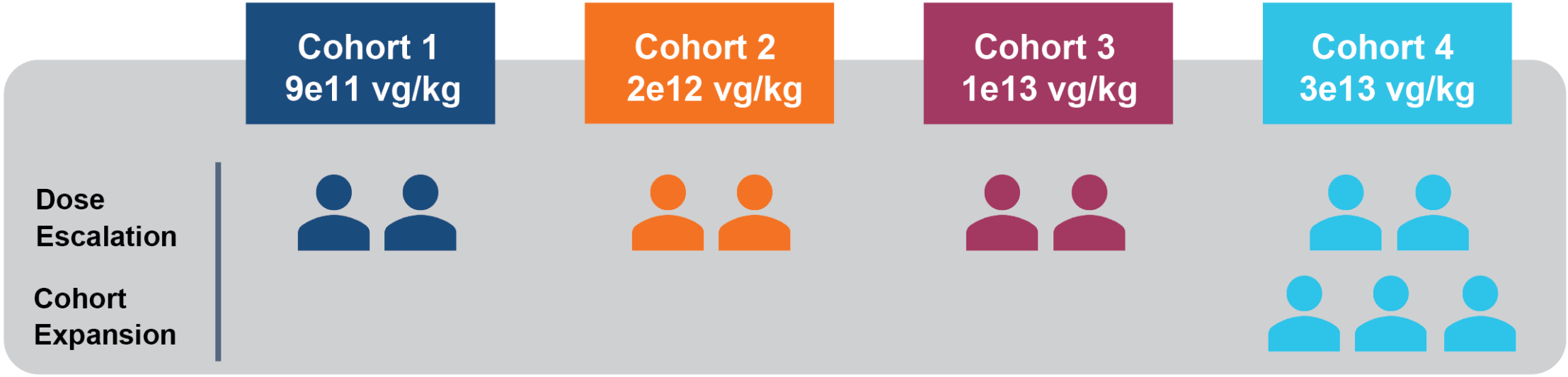
SECONDARY END POINTS

- 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.

Participants

- 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 1.5 × baseline value
- Safety and efficacy data of each cohort were reviewed by an independent safety monitoring committee prior to each dose escalation and before initiating cohort 4 expansion
- Follow-up duration ranges from 2 to 4 years after infusion



ALT, alanine aminotransferase; vg, vector genomes.

Baseline 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 (9.2)	35.5 (16.3)	32.5 (0.7)	27.2 (6.1)	30.3 (7.8)
	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)
	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: 01OCT2021
Max, maximum; min, minimum; SD, standard deviation; vg, vector genomes.

Safety Summary

- A total of 103 treatment-emergent AEs occurred in 11 patients
- 26 treatment-related AEs occurred in 6 participants, with the most common being:
  - 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; all resolved with intervention
  - LFT elevations were managed with tapering corticosteroids (median 58 days; range: 11–134 days)
- 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, which resolved by ≈12 hours post-infusion
- No confirmed FVIII inhibitor development occurred
- No thrombotic events were reported
- No 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.

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)	
	Participants, n	No. of Events	Participants, n	No. of Events	Participants, n	No. of Events
Any treatment-related event	2	5	4	21	6	26
Grade 3/4 AE	0	0	1[a]	1	1	1
ALT increased	2	3	3	10	5	13
AST increased	1	2	2	3	3	5
Pyrexia	0	0	3	3	3	3
Tachycardia	0	0	2	2	2	2
Myalgia	0	0	1	1	1	1
Hypotension	0	0	1	1	1	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)

Data cut: 01OCT2021

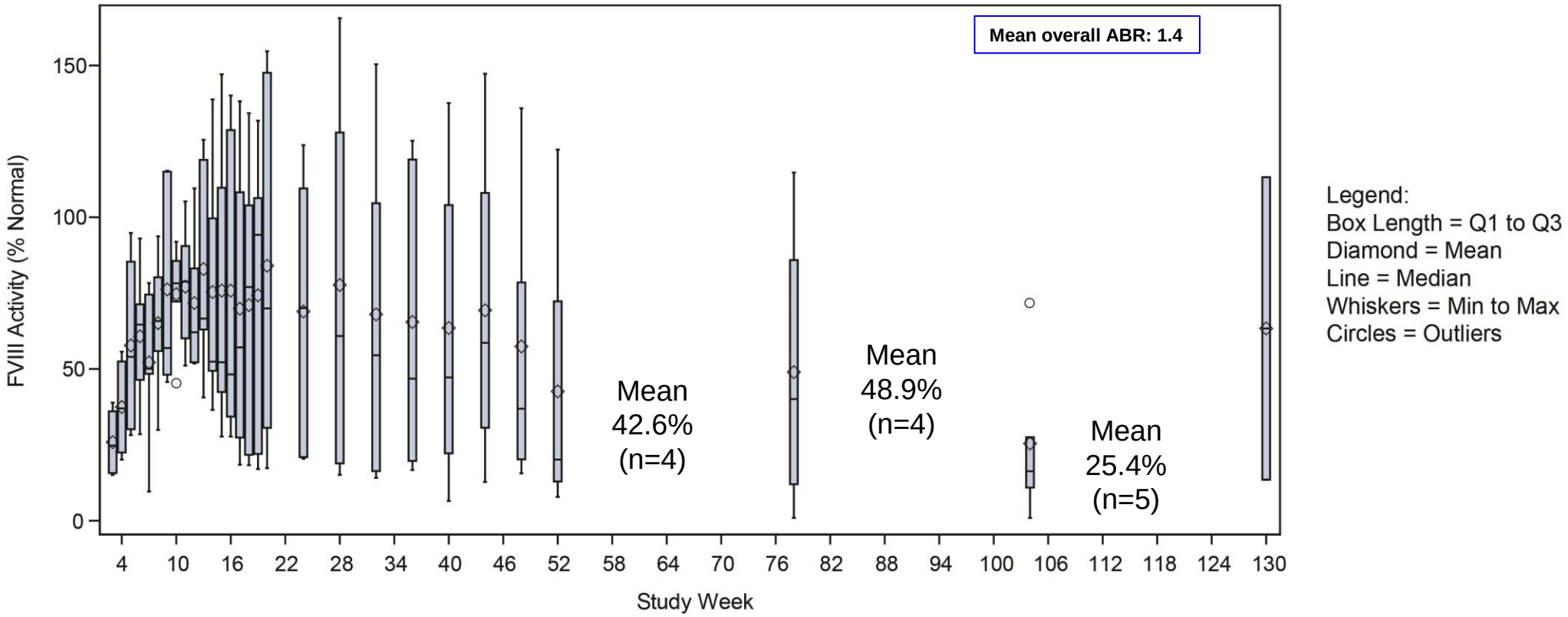
[a]One patient experienced grade 3 hypotension that was considered related to study drug and resolved with treatment.

AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; vg, vector genomes.

Efficacy: Cohort 4 (3e13 vg/kg)

- 0 bleeding events occurred in the first year post-infusion
- Mean overall ABR = 1.4 (n=5 participants with ≥2 years of follow-up)

FVIII Activity, as Measured at Central Laboratory With Chromogenic Assay



[a]Mild, >5% to <40% and normal range, >50%.
Latest available FVIII values from October 2021 data cut.
FVIII, factor VIII; vg, vector genomes.

Efficacy Summary: Cohort 4 (3e13 vg/kg)

- Mean ABR was 0.0 for the first year post-infusion, and was 1.4 throughout the total duration of follow-up to date
- Mean (SD) FVIII activity (% normal) at week 104 was 25.4 (27.5), as measured by the chromogenic clotting assay at the central laboratory
- Two participants experienced bleeding events necessitating treatment with exogenous FVIII, all bleeding events occurred after week 69 post-infusion
  - 8 treated bleeding events in 1 participant: 5 traumatic, 2 spontaneous, 1 unknown
  - 1 bleeding event in a target joint in 1 participant: circumstances unknown
- No participants in cohort 4 have resumed prophylaxis, with mean FVIII activity in the mild range through 104 weeks post-infusion

ABR calculated as: (number of all bleeding episodes starting 3 weeks after study drug infusion)/(observation period in years).
ABR, annualized bleeding rate; 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 a 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 has started and has enrolled >50% of patients

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

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