# Updated Follow-up of the High-Dose Cohort in the Alta Study, a Phase 1/2 Study of giroctocogene fitelparvovec (SB-525) Gene Therapy in Adults With Severe Hemophilia A

Thomas J. Harrington, MD[1]; Barbara A. Konkle, MD[2]; Kimo Stine, MD[3]; Nathan Visweshwar, MD[4]; Andrew D. Leavitt, MD[5]; Adam Giermasz, MD, PhD[6]; Steven Arkin, MD[7]; Annie Fang, MD, PhD[8]; Li-Jung Tseng, MBA, PhD[8]; Gregory Di Russo, MD[7]; Bettina M.Cockroft, MD, MBA[9]; Adrian Woolfson, MD, PhD[9]; Jeremy Rupon, MD, PhD[10]; Didier Rouy, MD, PhD[9]

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

Presented at the World Federation of Hemophilia (WFH) Virtual Summit, June 14–19, 2020

# Disclosures for:
# Thomas J. Harrington, MD

| Conflict | Disclosure |
|---|---|
| Research Support | Sangamo/Pfizer Inc. |
| Director, Officer, Employee | none |
| Shareholder | none |
| Honoraria | none |
| Advisory Committee | none |
| Consultant | none |
| | |

# Disclaimer

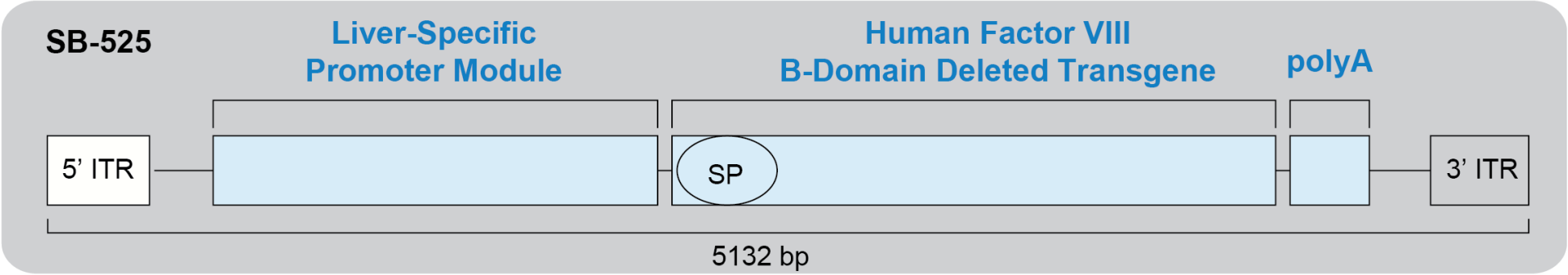
- Data in this presentation are presented “as-is” and potentially subject to change.

# Hemophilia A

- Characterized by increased bleeding caused by low levels of factor VIII (FVIII) activity resulting from mutations in the *F8* gene
- Treatment is currently based on replacement therapy with exogenous FVIII, along with emerging mimetic-based therapy
- Current treatments require frequent dosing to be effective, and involve intravenous (IV) or subcutaneous administration
- Maintenance of FVIII activity in the mild to normal range can improve the outcomes for patients with hemophilia A
- The wide therapeutic window and underlying single gene defect make hemophilia A an ideal candidate for gene therapy

# Giroctocogene fitelparvovec (SB-525) Gene Therapy for Hemophilia A

- Alta is a phase 1/2 dose-ranging, single-dose, multicenter study to assess the safety and tolerability of giroctocogene fitelparvovec (SB-525) in adult subjects (aged ≥18 years) with severe hemophilia A
- Giroctocogene fitelparvovec (SB-525) is a liver-tropic recombinant adeno-associated virus (rAAV6) vector carrying a B-domain–deleted *F8* gene that is delivered through a single IV infusion
- 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

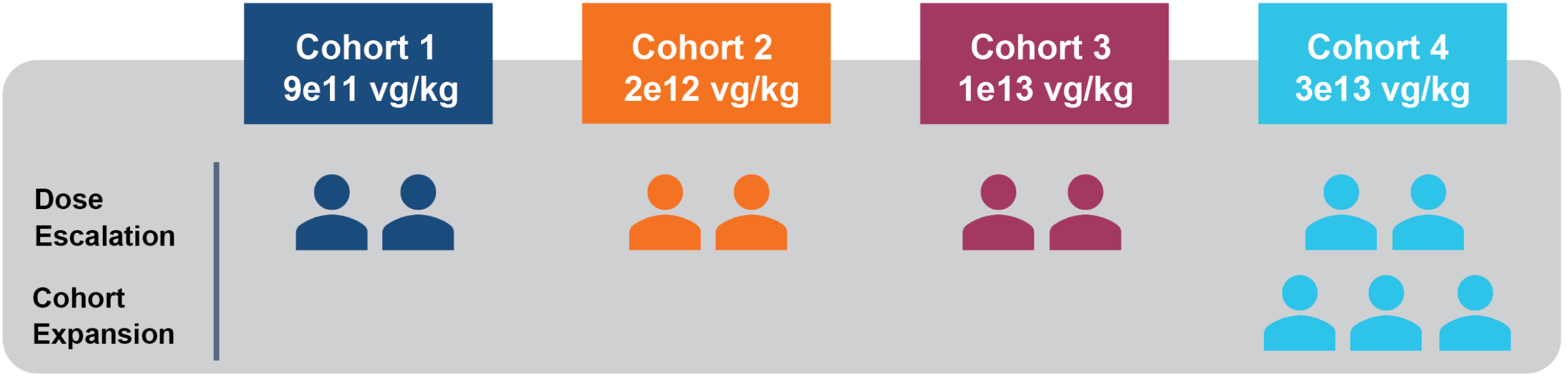


# Study End Points

- Primary end points
  - Safety and tolerability of SB-525, as assessed by the incidence of adverse events (AEs) and serious adverse events (SAEs) and by changes in clinical laboratory assessments, vital signs and electrocardiogram, and liver imaging
  - Changes in circulating FVIII activity
- Secondary end points
  - Change from baseline in the use of FVIII replacement therapy and frequency and severity of bleeding episodes
  - Measurement of FVIII inhibitor levels
  - Vector shedding in bodily fluids

# Study Status

- 4 dose cohorts of 2 subjects each and a high-dose cohort expansion of 3 subjects (total of 11 subjects dosed); no prophylactic steroid use
- Steroid treatment is initiated for alanine aminotransferase (ALT) elevation that exceeds 1.5x baseline value
- The 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



# Study Status, cont'd

## Patient Demographics

| Characteristic | | Cohort 1 9e11 vg/kg | Cohort 2 2e12 vg/kg | Cohort 3 1e13 vg/kg | Cohort 4 3e13 vg/kg | All Subjects |
|---|---|---|---|---|---|---|
| Age, years | n | 2 | 2 | 2 | 5 | 11 |
| | Mean (SD) | 30.5 (9.19) | 35.5 (16.26) | 32.0 (1.41) | 26.8 (6.30) | 30.0 (7.94) |
| | Median | 30.5 | 35.5 | 32.0 | 29.0 | 30.0 |
| | Min-max | 24, 37 | 24, 47 | 31, 33 | 18, 34 | 18, 47 |
| Gender, 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) |

Min-max, minimum-maximum.
Data cut: March 2020

# Safety Summary: Cohort 4 ($3x10^{13}$ vg/kg)

- 1 subject had a treatment-related serious adverse event (SAE) of grade 3 hypotension and grade 2 fever, with symptoms of headache and tachycardia occurring ≈6 hours after completion of the vector infusion, with resolution ≈12 hours postinfusion
- No additional treatment-related SAEs
- 4/5 subjects in the high dose cohort required corticosteroid treatment for elevations in liver transaminase (ALT/AST), which all resolved with intervention
  - 3 of the 4 subjects had subsequent elevations in liver transaminases after resolution of the initial increase and received a repeat course of corticosteroids, which all resulted in resolution
- FVIII activity levels were sustained in all cases, with no patients experiencing bleeding events or requiring FVIII infusions

# Safety Summary: Treatment-Related Adverse Events Cohort 4 ($3x10^{13}$ vg/kg)

| MedDRA Preferred Term | Cohort 4 3e13 vg/kg (N=5) | |
|---|---|---|
| | Subjects, n (%) | No. of Events |
| Any treatment-related event | 5 (100.0) | 42 |
| Alanine aminotransferase increased* | 3 (60.0) | 9 |
| Pyrexia | 4 (80.0) | 4 |
| Aspartate aminotransferase increased | 1 (20.0) | 2 |
| Tachycardia | 2 (40.0) | 2 |
| Fatigue | 1 (20.0) | 1 |
| Hypotension | 1 (20.0) | 1 |
| Myalgia | 1 (20.0) | 1 |

*One subject had an ALT increase as per central lab results, but Investigator has not reported increase as an Adverse Event

Data cut: March 2020

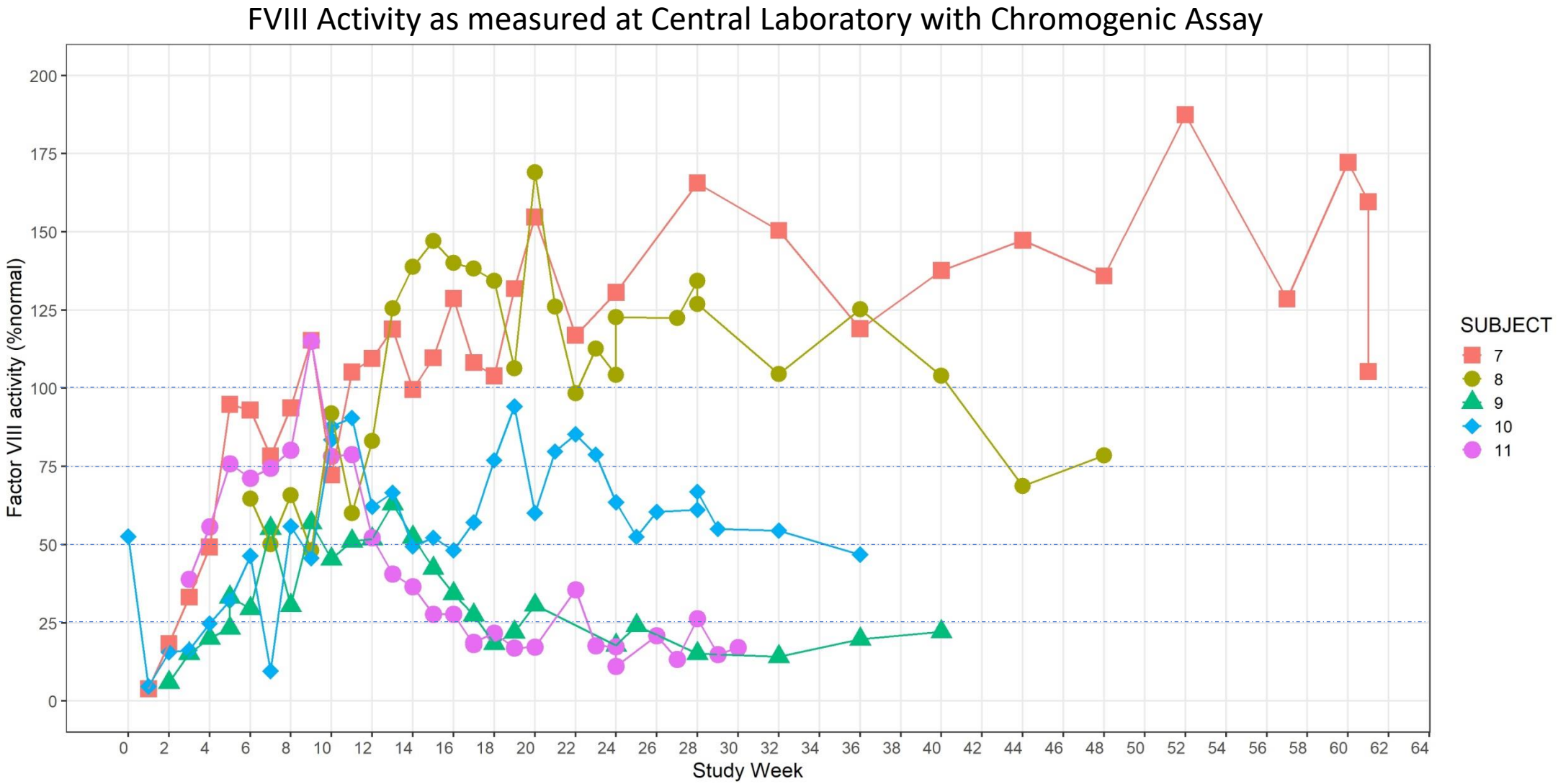
# ALT Elevations: Cohort 4 ($3x10^{13}$ vg/kg)

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

| Subject ID Number | Time of First ALT Elevation (Week) | Maximum ALT Value, U/L (Grade) | Steroids, >60mg (Weeks) | Steroids, Taper (Weeks) | FVIII levels (Chromo, IU/dL) at Start of Steroids | FVIII Levels (Chromo, IU/dl) at End of Taper | Time of Second ALT Elevation (Week) | Weeks of Steroids After Second Elevation |
|---|---|---|---|---|---|---|---|---|
| 7 | 4.5 | 91 (gr 1) | 3 | 11 | 94.8 | 108.2 | 48# | 16# |
| 8 | 12 | 66 (gr 1) | 1 | 16 | 83.1 | 112.6 | N/A | N/A |
| 10 | 5.5 | 63 (gr 1) | N/A* | 6 | 46.4 | 57.1 | 20 | 9 |
| 11 | 8 | 192 (gr 2) | 1.5 | 4 | 80.2 | 27.7 | 16 | 18 |

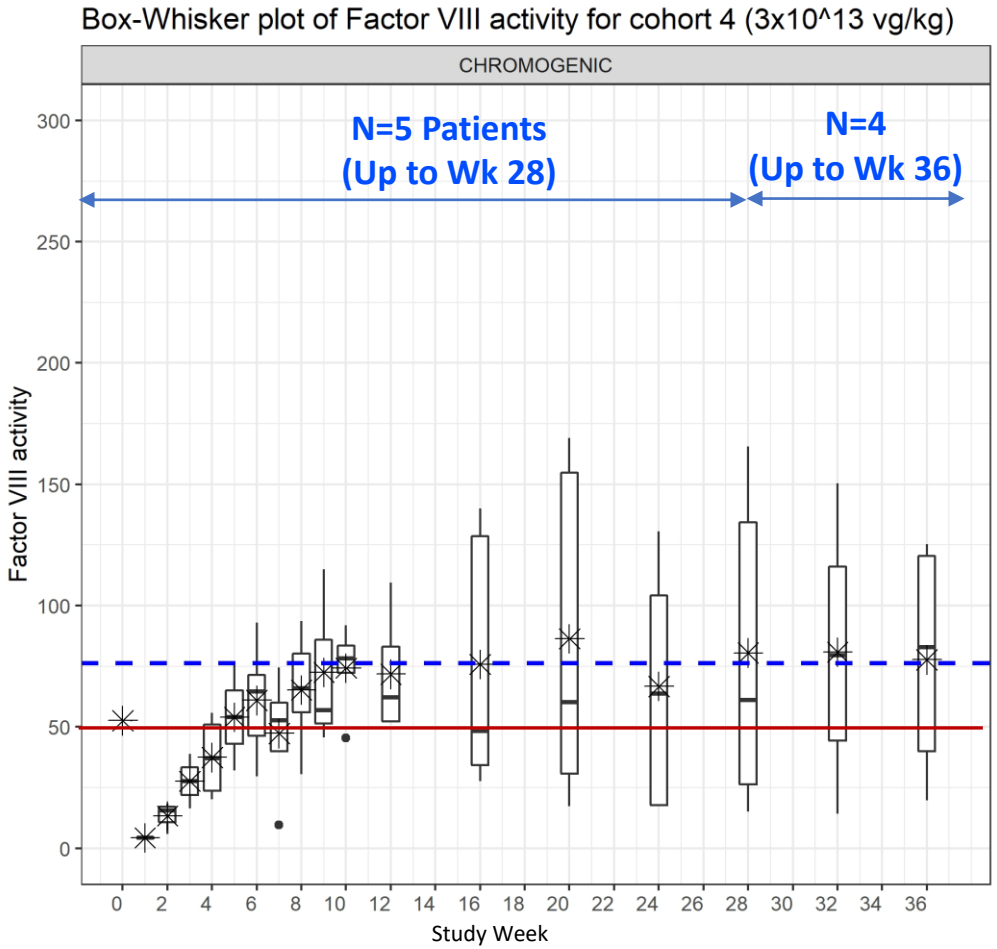
N/A: not applicable
*: Subject started at 60mg.
#: Subject had an additional isolated elevation of ALT at week 28 that was treated with corticosteroids for 1 week and then discontinued. Treatment was ongoing at the time of data cut.
Data cut March 2020

# Efficacy: Cohort 4 ($3x10^{13}$ vg/kg)




Latest available FVIII values from March 2020 data cut

# Efficacy: Cohort 4 ($3x10^{13}$ vg/kg)




50% Factor VIII activity (Lower bound of Normal)

Mean Factor VIII activity value from Week 9 to Week 36 (based on group mean)

* Mean (Box-Whisker plot)

Data cut: March 2020

# Efficacy: Cohort 4 ($3x10^{13}$ vg/kg)

- Steady-state FVIII activity achieved by week 9 post infusion
- Subjects have been followed for 33-65 weeks, FVIII activity values available up to week 30 and up to week 61
- Median steady-state (of geometric means since week 9) FVIII activity level 64.2% via central laboratory chromogenic assay (CA; previously reported that CA tends to correlate better with FVIII antigen level than one-stage clotting assay (OS))
- No bleeding events
- No FVIII infusions beyond initial use of prophylactic factor

# Conclusions

- Cohort 4 ($3x10^{13}$ vg/kg):
  - With follow-up ranging 33 to 65 weeks, data continues to show that giroctocogene fitelparvovec (SB-525) is generally well tolerated
  - Sustained FVIII activity levels
  - No use of exogenous FVIII beyond week 3 post infusion
  - No bleeding events
  - 1 treatment related SAE during vector infusion, no additional treatment related SAEs
- Follow-up for Cohorts 1-3 extends up to over 2 years with no safety signals
- The Ph1/2 study is ongoing and supports further development of giroctocogene fitelparvovec (SB-525)
- Phase 3 lead-in study is ongoing