

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

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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

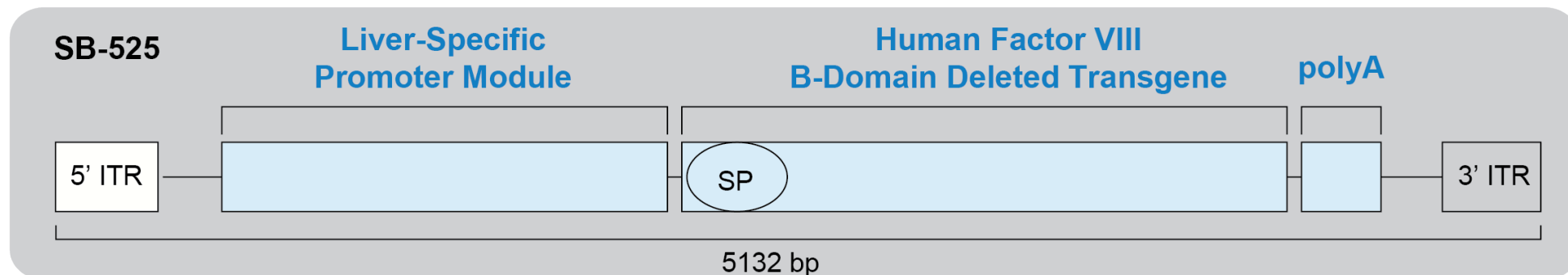
- Data in this presentation are presented “as-is” and potentially subject to change.
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Hemophilia A

- 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
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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

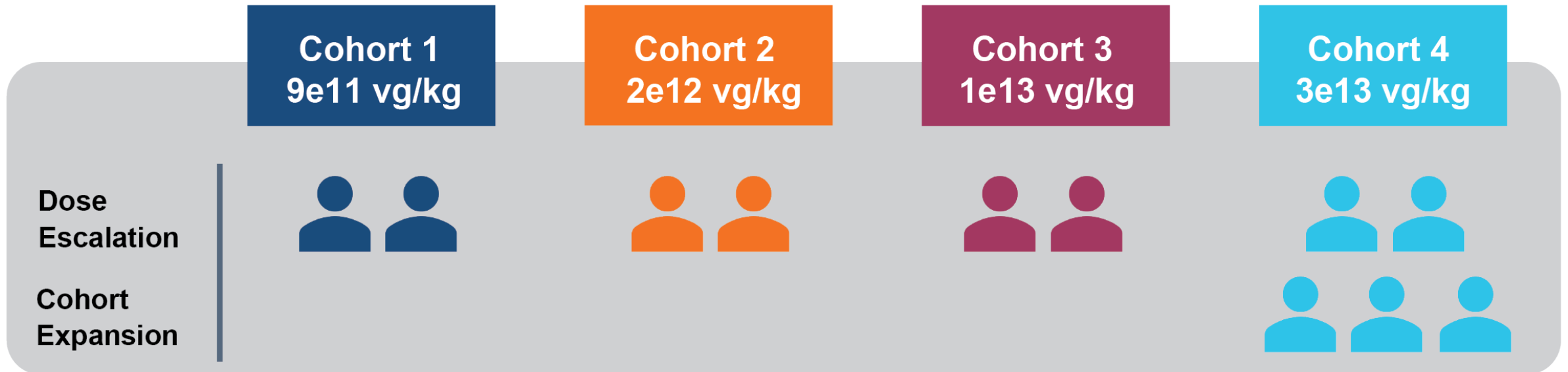


Study End Points

- 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
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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)

Safety Summary: Cohort 4 (3×10^{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 \approx 6 hours after completion of the vector infusion, with resolution \approx 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
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Safety Summary: Treatment-Related Adverse Events

Cohort 4 (3×10^{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 (3×10^{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

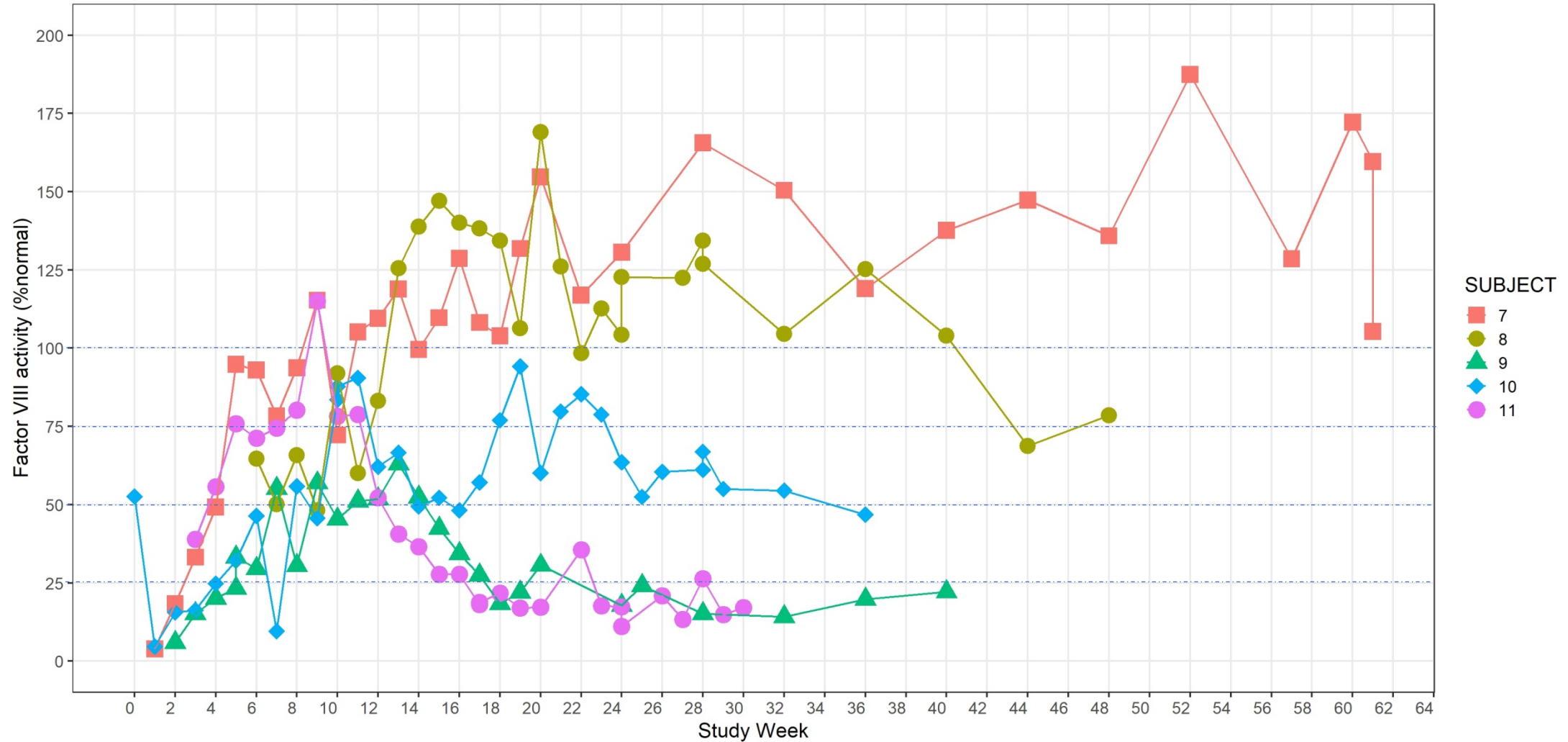
*: Subject started at 60mg.

#: 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 (3×10^{13} vg/kg)

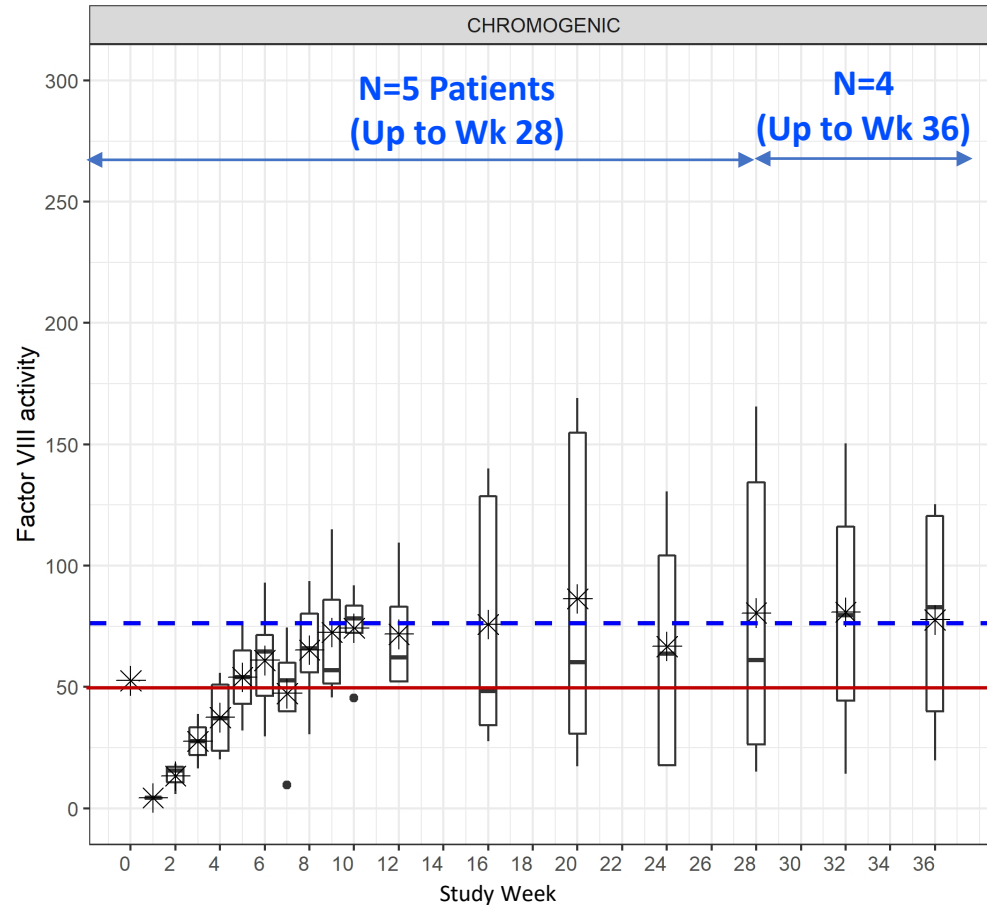
FVIII Activity as measured at Central Laboratory with Chromogenic Assay



Latest available FVIII values from March 2020 data cut

Efficacy: Cohort 4 (3×10^{13} vg/kg)

Box-Whisker plot of Factor VIII activity for cohort 4 (3×10^{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 (3×10^{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
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Conclusions

- Cohort 4 (3×10^{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
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