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Initial results of the Alta study, a phase 1/2, open label, adaptive, dose-ranging study to assess the safety and tolerability of SB-525 gene therapy in adult subjects with hemophilia A

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Hemophilia A

- Rare blood disorder caused by an *F8* variant resulting in insufficient Factor VIII (FVIII) activity
- Monogenic disorder with a clear cause and effect relationship
- Wide therapeutic index: a modest increase in FVIII activity can improve patient outcomes
- Efficacy easy to assess: factor levels, factor usage and bleeding episodes
- Ideal candidate for gene therapy, which has the potential to eliminate the need for factor replacement

Alta Hemophilia A Gene Therapy Study

- Alta is a Phase 1/2 dose-ranging, single-dose, multicenter study to assess the safety and tolerability of SB-525 in adult subjects (>18yrs) with severe hemophilia A
- SB-525 is a liver-targeted recombinant adeno-associated virus (rAAV6) vector carrying a B-domain deleted *F8* gene which is delivered through a single intravenous infusion
- Key exclusion criteria:
  - Neutralizing activity to AAV6 capsid
  - History of hypersensitivity response to FVIII
  - History of liver dysfunction
  - Contraindication to steroids

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Study Endpoints

Protocol

SB-525-1603

US IND #17250

Clinicaltrials.gov, NCT03061201

Primary Endpoints:

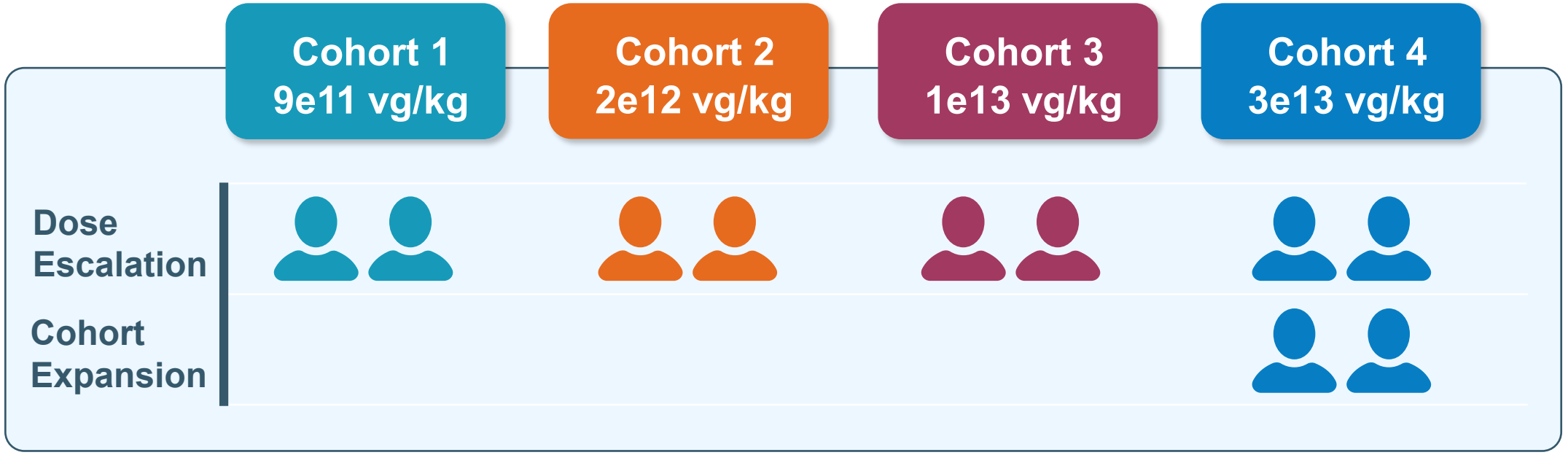
- Safety and tolerability of SB-525 as assessed by incidence of adverse events (AEs) and serious adverse events (SAEs), and changes in clinical laboratory assessments
- Changes in circulating FVIII activity

Secondary Endpoints:

- Change from baseline in use of FVIII replacement therapy and frequency and severity of bleeding episodes
- Measurement of FVIII inhibitor level

Study Status

- Four dose cohorts with 2 subjects each and a high-dose cohort expansion of 2 subjects (total of 10 subjects dosed). No prophylactic steroid usage
- The safety and efficacy data of each cohort was reviewed by an independent safety monitoring committee prior to each dose escalation and prior to initiating cohort 4 expansion



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Patient Demographics

Subject characteristics		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=4)	All Subjects (N=10)
Age (Yrs)	Mean (SD)	30.5 (9.19)	35.5 (16.26)	32.0 (1.41)	27.8 (6.85)	30.7 (8.00)
	Median	30.5	35.5	32.0	29.5	30.5
	Min-Max	24, 37	24, 47	31, 33	18, 34	18, 47
Sex n (%)	Male	2 (100)	2 (100)	2 (100)	4 (100)	10 (100)
Race n (%)	Asian	-	1 (50)	-	-	1 (10)
	White	2 (100)	1 (50)	2 (100)	3 (75)	8 (80)
	Other (White/Black)	-	-	-	1 (25)	1 (10)

N= Total number of subjects, n= number of subjects in each group

Data cut-off date: 30 MAY 2019

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Safety Summary

- Treatment-related SAEs of hypotension (grade 3) and fever (grade 2) in one Cohort 4 subject occurred 6 hrs following SB-525 infusion. Fully resolved with treatment within 24 hrs
  - Based on the temporal association, assessed as related to study treatment
  - No similar hypotension observed in subsequent 3 subjects dosed
- In the 3e13 vg/kg cohort two subjects experienced a transient grade 1 alanine aminotransferase elevation (>1.5 x baseline) managed with a tapering course of oral steroids. Neither resulted in a loss of FVIII activity levels

Data cut-off date: 30 MAY 2019

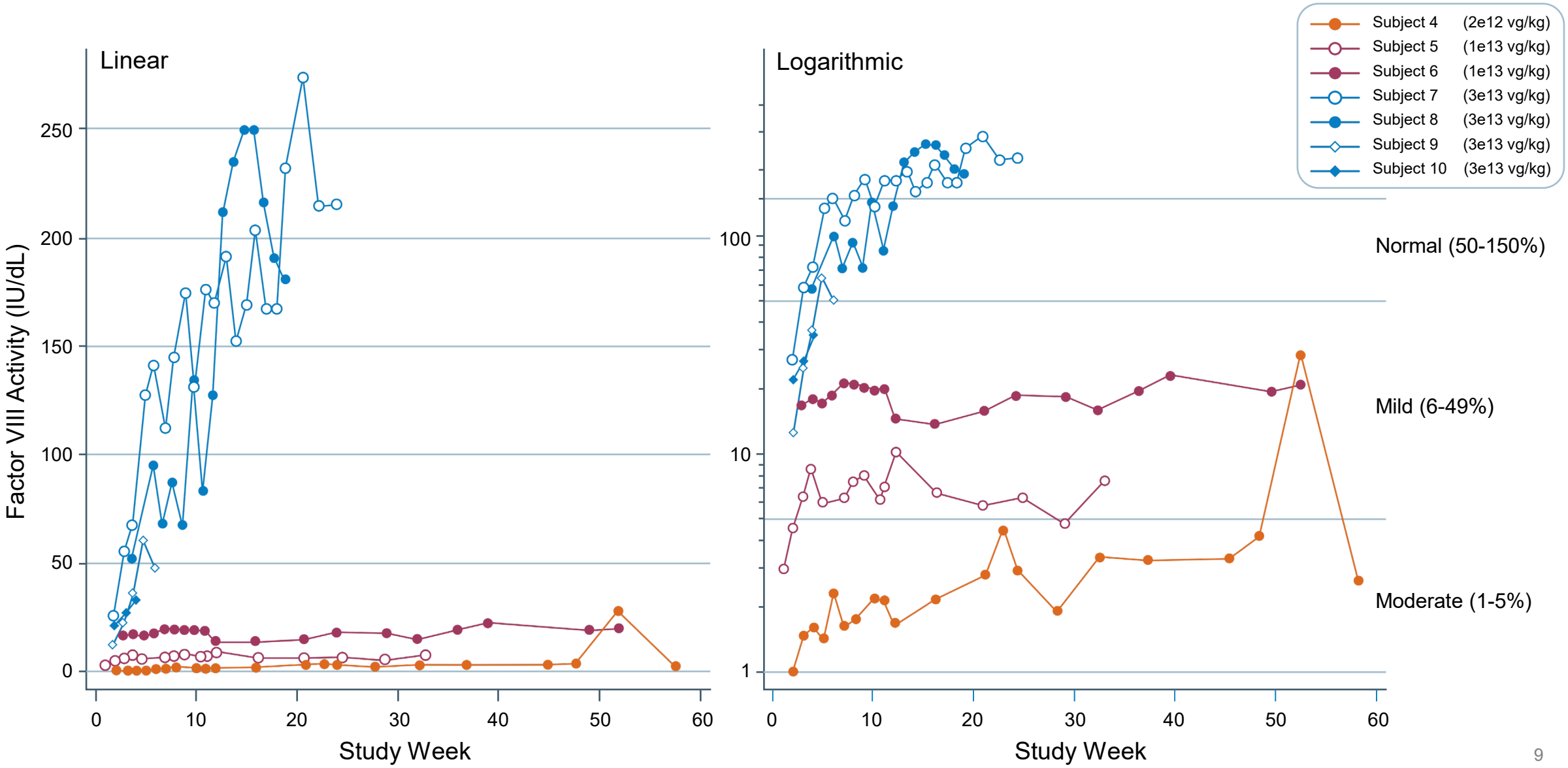
Treatment-Related Adverse Event (TRAE) Summary

MedDRA Preferred Term	Cohort 1 9e11 vg/kg (N=2) n(%)[T]	Cohort 2 2e12 vg/kg (N=2) n(%)[T]	Cohort 3 1e13 vg/kg (N=2) n(%)[T]	Cohort 4 3e13 vg/kg (N=4) n(%)[T]	Overall (N=10) n(%)[T]
Any treatment-related event	0	2 (100) [4]	0	3 (75) [8]	5 (50) [12]
Alanine aminotransferase increased	0	2 (100) [3]	0	1 (25) [1]	3 (30) [4]
Pyrexia	0	0	0	3 (75) [3]*	3 (30) [3]
Aspartate aminotransferase increased	0	1 (50) [1]	0	0	1 (10) [1]
Fatigue	0	0	0	1 (25) [1]	1 (10) [1]
Hypotension	0	0	0	1 (25) [1]**	1 (10) [1]
Myalgia	0	0	0	1 (25) [1]	1 (10) [1]
Tachycardia	0	0	0	1 (25) [1]	1 (10) [1]

N= Total number of subjects in each treatment group, n= number of subjects in each system organ class (SOC), [T]= total number of treatment-related adverse events. *All 3 events were reported as Grade 2 ** Grade 3 event reported

Data cut-off date: 30 MAY 2019

Factor VIII activity: One-stage



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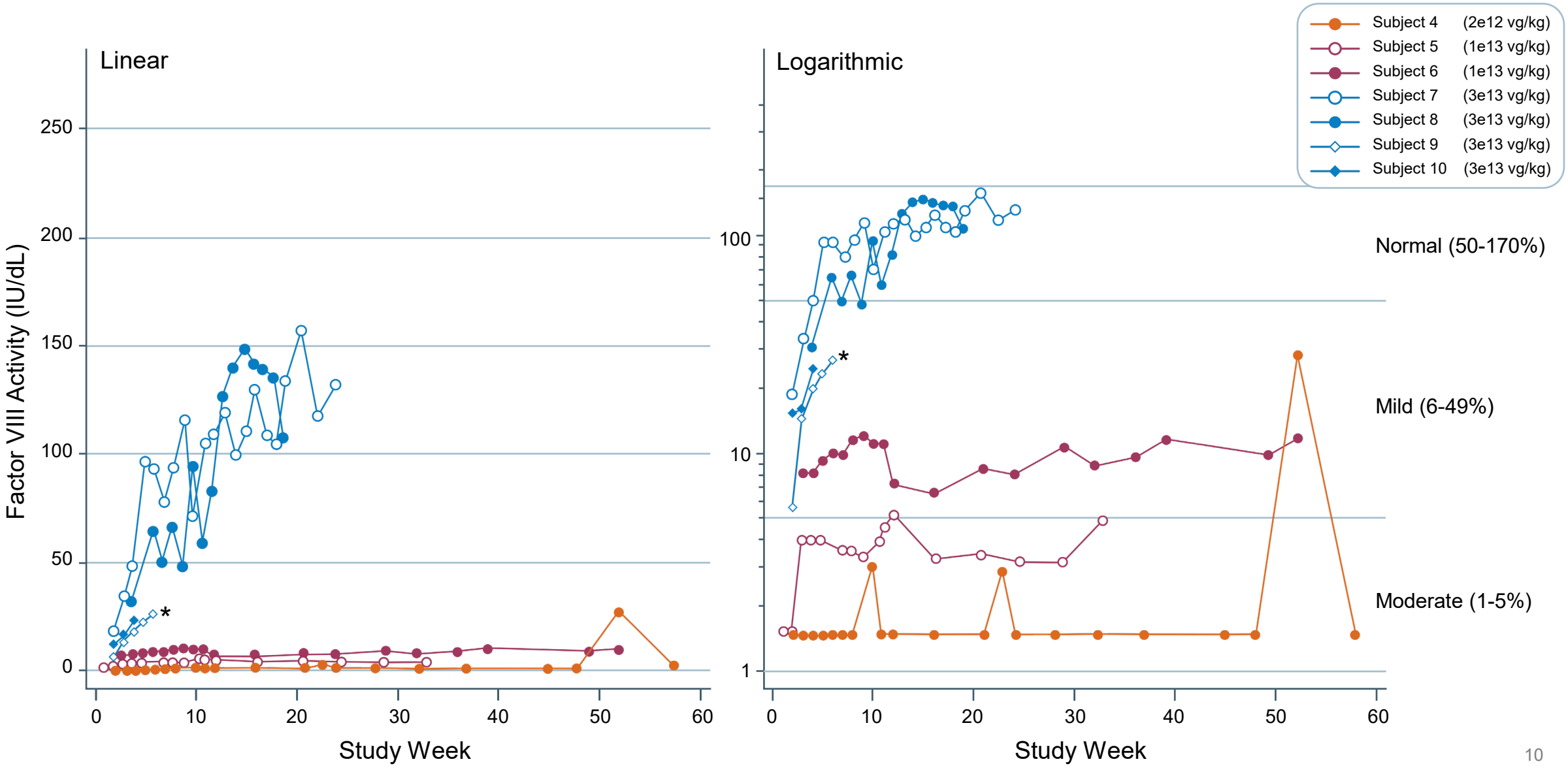
Factor VIII activity: Chromogenic



* Subsequent to the data cut used for the ISTH presentation, Subject 9 attained normal levels at week 7

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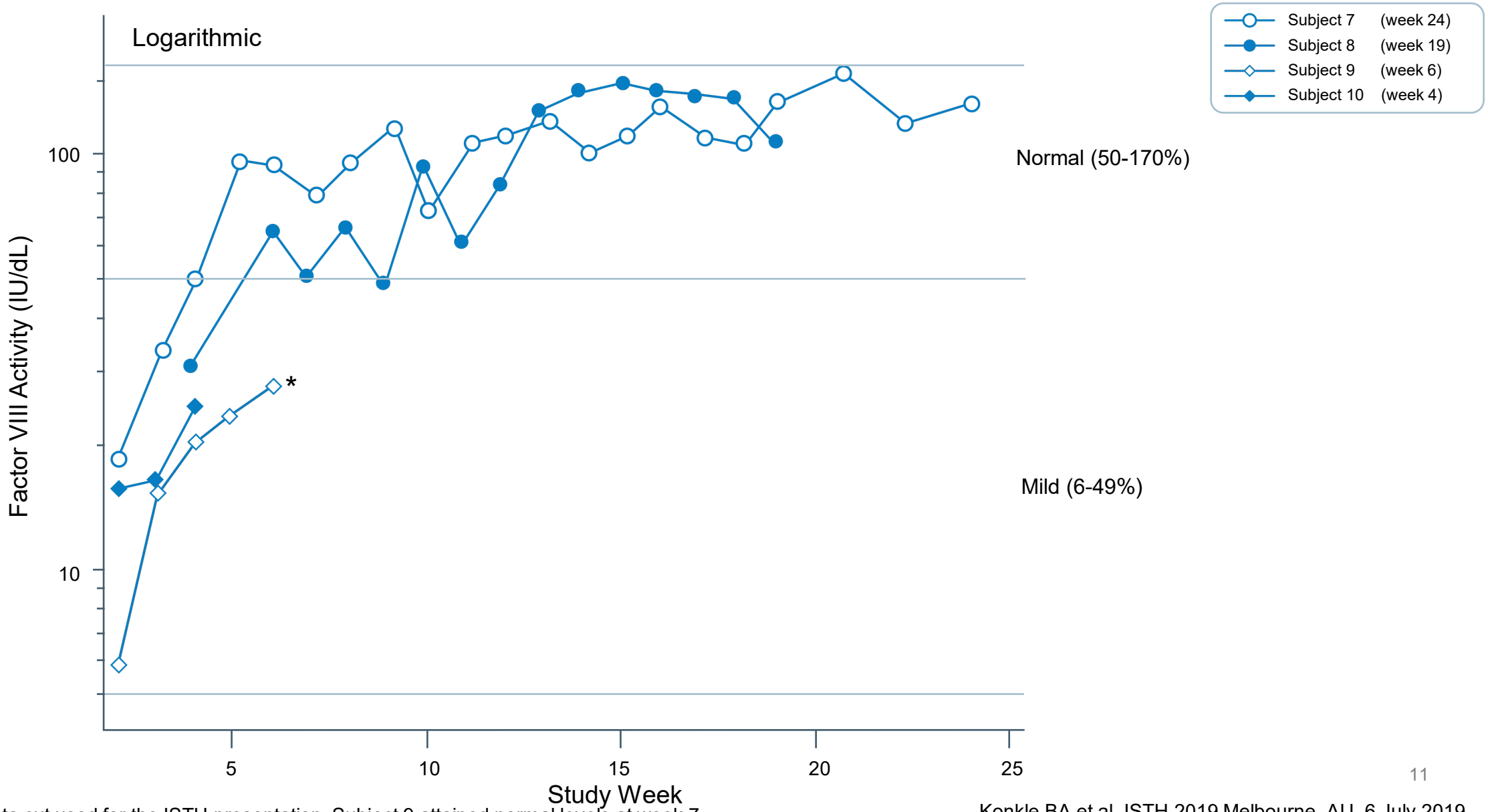
Factor VIII activity: Chromogenic, Cohort 4 (3e13 vg/kg)



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Spontaneous Bleeding Episodes

Dose Cohort (dose vg/kg)	Subject	Follow-Up (weeks)	Bleeding Episodes ≥3 weeks Post Treatment
1 (9e11)	1	93	7
1 (9e11)	2	83	5
2 (2e12)	3	73	8
2 (2e12)	4	66	5
3 (1e13)	5	50	5
3 (1e13)	6	41	0
4 (3e13)	7	24	0
4 (3e13)	8	18	0
4 (3e13)	9	5	0
4 (3e13)	10	2	n/a*

*n/a: < 3 weeks of follow-up at time of data cut

Data cut-off date: 30 MAY 2019

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Factor VIII Replacement Usage

Dose Cohort (dose vg/kg)	Subject	Follow-Up (weeks)	Factor VIII Prophylactic Regimen Prior to Dosing	Factor VIII Infusions ≥ 3 weeks Following SB-525 Treatment
1 (9e11)	1	93	2/Week	115
1 (9e11)	2	83	2/Week	26
2 (2e12)	3	73	2/Week	13
2 (2e12)	4	66	3/Week	9
3 (1e13)	5	50	Every Other Day	11
3 (1e13)	6	41	Every Other Day	0
4 (3e13)	7	24	Every 4 Days	0
4 (3e13)	8	18	Every Other Day	1*
4 (3e13)	9	5	Every 3 Days	0
4 (3e13)	10	2	Every 3 Days	n/a§

*Prophylactic coverage stopped 3 weeks and 2 days after SB-525 administration, §n/a: < 3 weeks of follow-up at time of data cut

Data cut-off date: 30 MAY 2019

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Conclusions

- SB-525 was generally well-tolerated in all 10 subjects with severe hemophilia A treated at doses ranging from 9e11 vg/kg to 3e13 vg/kg
- All treatment-related ALT elevations were grade 1 and none were associated with a loss of FVIII expression
- Dose-dependent increases in FVIII activity over baseline were observed. Subjects treated at the 3e13 vg/kg dose for at least 7 weeks achieved normal range FVIII activity
- Lower-dose cohorts indicate durable FVIII activity up to 52 weeks of follow-up
- Subjects treated at 3e13 vg/kg did not require FVIII replacement therapy following the initial prophylactic period post-SB-525 administration
- No bleeding events have been observed in any of the 4 subjects treated at the 3e13 vg/kg dose

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  - Dr. Thomas Harrington, University of Miami Miller School of Medicine, Miami, FL
  - Dr. Andrew Leavitt, Department of Laboratory Medicine, University of California, San Francisco, CA, Department of Medicine, University of California, San Francisco, CA
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