Updated Follow-up 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

Poster #2060

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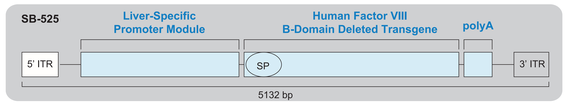
Hemophilia A

- Hemophilia A is a rare blood disorder caused by an *F8* variant resulting in insufficient activity of Factor VIII (FVIII)
- Its present treatment is demanding and does not fully avoid bleeding episodes
- This single-gene disorder has a clear cause-and-effect relationship, with a wide therapeutic window. Low concentrations of FVIII will improve outcomes; high concentrations (>40% of normal) provide a potential for cure
- Efficacy of the therapy can be assessed through tracking of factor levels, bleeding episodes, and FVIII use
- The *F8* gene is therefore an ideal candidate for gene therapy, which has the potential to eliminate the need for factor replacement

Alta Gene Therapy for Hemophilia A

- Alta is a Phase 1/2 dose-ranging, single-dose, multicenter study to assess the safety and tolerability of SB-525 in adult subjects (>18 years old) with severe hemophilia A
- SB-525 is a liver-targeted recombinant adeno-associated virus (rAAV6) vector carrying a B-domain deleted *F8* gene that 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



ITR, inverted terminal repeats.

Study Endpoints

Primary Endpoints:

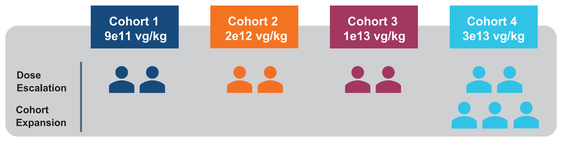
- Safety and tolerability of SB-525 as assessed by incidence of adverse events (AEs) and serious adverse events (SAEs) and changes in clinical laboratory assessments
- Changes in circulating FVIII activity

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 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



Patient Demographics

Patient 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=5)	All Subjects (N=11)
Age, years	n	2	2	2	5	11
	Mean (SD)	30.5 (9.19)	35.5 (16.26)	32.0 (1.41)	26.80 (6.30)	30.00 (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
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)
Ethnic, 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; N, total number of subjects; n, number of subjects in each group.
Data cutoff date: October 17, 2019.

Safety Summary

- Treatment-related SAEs of hypotension (grade 3) and fever (grade 2) in one Cohort 4 subject occurred 6 hours after SB-525 infusion, and fully resolved with treatment within 24 hours
  - Based on the temporal association, these SAEs were assessed by the investigator as related to study treatment
  - Following implementation of additional supportive care guidelines, no similar severity events were observed in the subsequent 4 subjects dosed
- In the 3e13 vg/kg cohort, 4 subjects experienced a transient low grade ALT elevation (>1.5x baseline) managed with a tapering course of oral steroids. These elevations were not associated with a loss of FVIII expression

Treatment-Related Adverse Event Summary

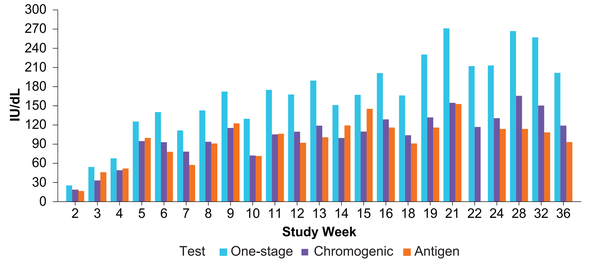
MedDRA Preferred Term	Cohort 1 9e11 vg/kg (N=2) n (%) [T]	Cohort 2 2e12 vg/kg (N=2) n (%) [T]	Cohort 3 1e13 vg/kg (N=2) n (%) [T]	Cohort 4 3e13 vg/kg (N=5) n (%) [T]	All Subjects (N=11) n (%) [T]
Any treatment-related event	0	2 (100) [4]	0	4 (80.0) [12]	6 (54.5) [16]
Alanine aminotransferase increased	0	2 (100) [3]	0	2 (40.0) [3]	4 (36.4) [6]
Pyrexia	0	0	0	3 (60.0) [3]	3 (27.3) [3]
Aspartate aminotransferase increased	0	1 (50) [1]	0	1 (20.0) [1]	2 (18.2) [2]
Tachycardia	0	0	0	2 (40.0) [2]	2 (18.2) [2]
Fatigue	0	0	0	1 (20.0) [1]	1 (9.1) [1]
Hypotension	0	0	0	1 (20.0) [1]	1 (9.1) [1]
Myalgia	0	0	0	1 (20.0) [1]	1 (9.1) [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.
Each subject is counted only once for each applicable specific adverse event. A subject with multiple adverse events within a system organ class is counted only once for that system organ class.
Table is sorted in descending order. Data cutoff date: October 17, 2019.

Efficacy Summary

FVIII Expression by One-Stage, Chromogenic, and FVIII Antigen ELISA Assays

- Antigen concentrations are consistent with FVIII activity as measured with the chromogenic assay
- Results for one representative subject (subject 7) are shown: Other subjects show the same relationship between assays



FVIII antigen is based on standardization curve using a Xyntha standard

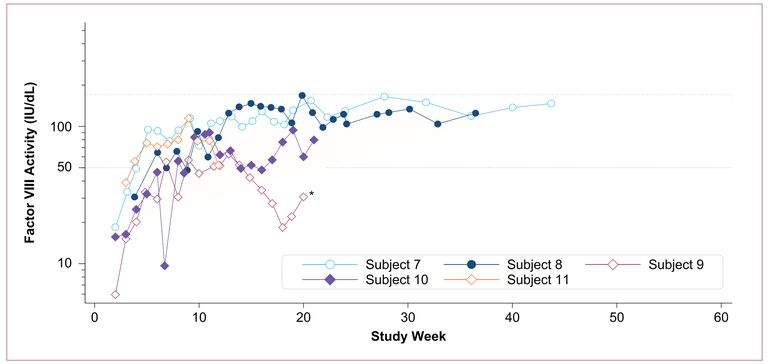
ALT Elevation Did Not Result in Loss of FVIII Expression

4 out of 5 subjects in the high dose cohort had an ALT elevation

Subject number	Time of first ALT elevation (week)	Maximum ALT value (U/L / grade)	Steroids high dose (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	98 (Gr 1)	5	7.5	94.8	108.2	28.5	1.5*
8	12	66 (Gr 1)	2	9	83.1	112.6	N/A	N/A
10	5.5	63 (Gr 1)	5	6	46.4	57.1	20	4#
11	8	192 (Gr 2)	2.5	4.5	80.2	Pending	N/A	N/A

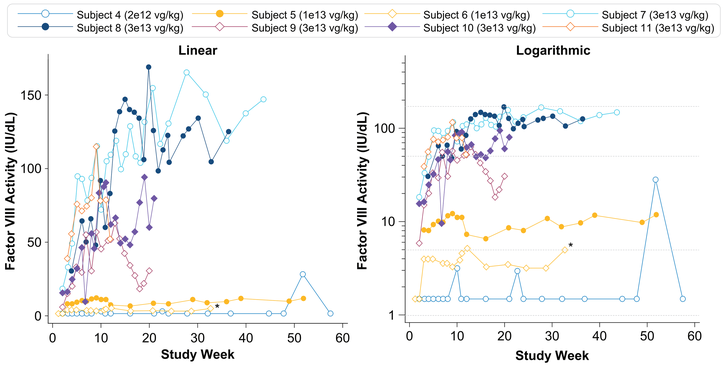
*After the end of the second course of steroids, the FVIII level was 150.4 IU/dL.
#Ongoing.

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



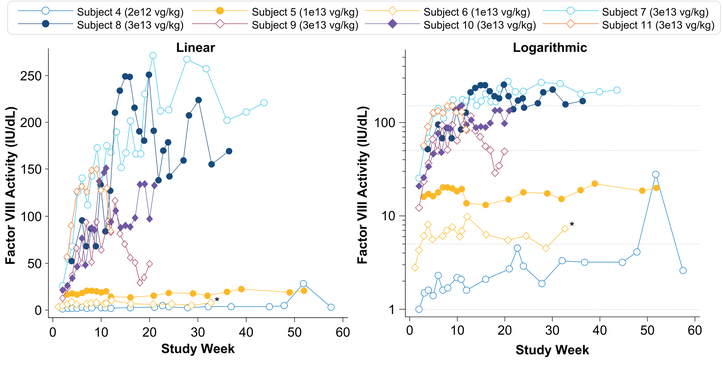
*von Willebrand factor levels for that subject dropped from 118% at week 1 to 48% at week 16
FVIII values with sample dates prior to treatment and up to 1 week after the treatment date or with sample dates within 3 days after an FVIII infusion are excluded.
Data cutoff date: October 17, 2019.

Factor VIII Activity: Chromogenic



FVIII values with sample dates prior to treatment and up to 1 week after the treatment date or with sample dates within 3 days after an FVIII infusion are excluded.
Data cutoff date: October 17, 2019.
*Subject missed follow-up visits and is no longer in contact with the site.

Factor VIII Activity: One-stage



FVIII values with sample dates prior to treatment and up to 1 week after the treatment date or with sample dates within 3 days after an FVIII infusion are excluded.
Data cutoff date: October 17, 2019.
*Subject missed follow-up visits and is no longer in contact with the site

All Treated Bleeding Episodes

Dose Cohort (dose vg/kg)	Subject	Follow-up (weeks)	Bleeding Episodes ≥3 Weeks Post Treatment
1 (9e11)	1	112	7
1 (9e11)	2	103	5
2 (2e12)	3	93	8
2 (2e12)	4	86	5
3 (1e13)	5	70	10
3 (1e13)	6	61	0
4 (3e13)	7	44	0
4 (3e13)	8	37	0
4 (3e13)	9	24	0
4 (3e13)	10	22	0
4 (3e13)	11	12	0

Bleeding episodes are being counted 21 days post dosing.
Days post dosing = October 17, 2019 - dosing day.

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	112	2/week	115
1 (9e11)	2	103	2/week	26
2 (2e12)	3	93	2/week	13
2 (2e12)	4	86	3/week	9
3 (1e13)	5	70	Every other day	17
3 (1e13)	6	61	Every other day	0
4 (3e13)	7	44	Every 4 days	0
4 (3e13)	8	37	Every other day	1*
4 (3e13)	9	24	Every 3 days	0
4 (3e13)	10	22	Every 3 days	0
4 (3e13)	11	12	2/week	0

*Prophylactic coverage stopped 3 weeks and 2 days after SB-525 administration.
Factor VIII infusions are being counted 21 days post dosing.
Days post dosing = October 17, 2019 - dosing day.

Conclusions

- SB-525 was generally well tolerated in all 11 subjects with severe hemophilia A treated at doses ranging from 9e11 vg/kg to 3e13 vg/kg
- To date, all treatment-related ALT elevations were low grade, 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 achieved normal-range FVIII activity after 5 to 7 weeks
- Lower-dose cohorts indicate durable FVIII activity up to 52 weeks of follow-up
- No bleeding events have been observed in any of the 5 subjects treated at the 3e13 vg/kg dose
- No subject treated at the 3e13 vg/kg dose required factor replacement following initial use of prophylactic factor
- The lead-in portion of a planned Phase 3 registration study with SB-525 in patients with severe Hemophilia A is currently ongoing

Acknowledgments

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