Seroprevalence and seroconversion among people with Hemophilia A in the United States: Observations from the SAAVY (Seroprevalence of **AAV** Antibody) study

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Population at 3-month

follow-up

n = 45

AAV+

Population assessed for

eroconversion at 3-month

follow-up

AAV5, n = 27 • AAV5, n = 18

AAV8. n = 29
AAV8. n = 10

of baseline AAV serostatus

AAV-

Background

- Pre-existing immunity against adeno-associated virus (AAV) serotypes is present in the people with hemophilia A (PwHA) population¹ and can restrict AAV-mediated gene therapy eligibility^{2,3}
- Data on seroprevalence among PwHA are increasing, although seroconversion data are limited
- Here, we describe results from the SAAVY study (BMN 270-701). which aimed to quantify the seroprevalence of antibodies to selected AAV serotypes (AAV5, AAV6, and AAV8), including antibody titers. and seroconversion over a 3- or 6-month period among PwHA

Methods

Study design

- SAAVY was a patient-centered, decentralized, randomized. prospective, observational study
- In an effort to make trial participation patient-friendly, SAAVY employed unified virtual study coordination and a convenient mobile app to enable remote recruitment and demographic collection across the US
- To remove the burden of traveling to traditional trial sites, participants were able to attend a network of 1800+ patient service centers (PSCs) throughout the US to provide blood samples
- After visiting a PSC for their initial blood draw for seroprevalence and providing self-reported data of interest via a custom mobile app, participants were randomized to a 3- or 6-month follow-up date for a second blood draw for seroconversion and self-reported data collection (Figure 1)

Participants

- Eligibility criteria summary
- Age ≥18 years - Hemophilia A (mild, moderate, or severe)
- Not previously treated with an AAV-based gene therapy

Study assessments

- Seroprevalence and antibody titer results for AAV5, AAV6, and AAV8 serotypes at baseline
- Seroconversion results were based on serostatus at baseline
- Converting from AAV antibody negative (AAV-) to AAV antibody positive (AAV+) or AAV+ to AAV-

Figure 1. Study implementation



rus: HTC, hemophilia tre ent center: PAG, patier cacy group; PSC, pat

Results

Participants

- Participant baseline demographics and clinical characteristics are shown in Table 1
- Of the 106 participants who provided a baseline sample. 20 were lost to follow-up (Figure 2)

Table 1. SAAVY participant demographics and baseline characteristics

Parameter	Overall population (n = 106)
Mean age ± SD (years)	45 ± 15
Age, n (%)	
≥18 to 30	12 (11.3)
≥30 to 50	48 (45.3)
≥50	46 (43.4)
Hemophilia A severity, n (%)	
Severe	50 (47.2)
Moderate	20 (18.9)
Mild	36 (33.9)
Race, n (%)	
American Indian or Alaska Native	3 (2.8)
Asian	6 (5.7)
Black or African American	3 (2.8)
White	69 (65.1)
Other, missing, or not provided ^a	25 (23.6)
Region of US, n (%)	
Northeast	23 (21.7)
South	35 (33.0)
West	32 (30.2)
Midwest	16 (15.2)
Where you live, n (%)	
Large city/urban area	25 (23.6)
Suburb area near a large city	42 (39.6)
Small city or town	20 (18.9)
Rural area	7 (6.6)
Missing	12 (11.3)
Processing (n. 1971) for each individual actions (N. 1. 17. 17. 17.	a sector for an annual sector data different

Race values (n [%]) for each individual category within the "other, missing, or not provided" categor were as follows: "other," 9 (8.5); "missing," 12 (11.3); "not provided due to patient privacy rules," 4 (3.8) SD_standard deviation

Figure 2. Distribution of participants following randomization

pulation at ba

n = 106

+

Randomization

Population at 6-month

follow-up

n = 41

AAV-

Population assessed for

seroconversion at 6-month

follow-up

AAV6, n = 23
AAV6, n = 18

AAV/8 n = 19 • AAV/8 n = 22

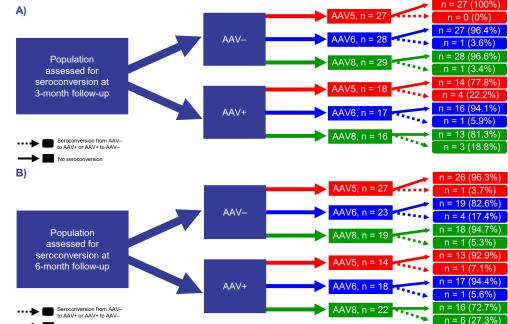
AAV+

AAV seroconversion



the 3- and 6-month follow-up visits

A)



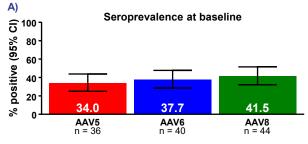
AAV seroprevalence and titers Seroprevalence was the lowest for AAV5, relative to AAV6 and AAV8, in PwHA at baseline (Figure 3A)

Sample-size values (n) for participants assessed for seroconversion at each follow-up time point are reflective

AAV-, adeno-associated virus antibody negative; AAV+, adeno-associated virus antibody positive; AAV5/6/8. adeno-associated virus serotype 5/6/8.

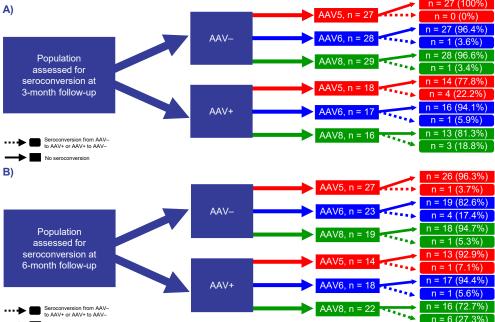
Antibody titers at baseline were lowest for AAV5, followed by AAV8 and AAV6 (Figure 3B)

Figure 3. AAV A) seroprevalence and B) antibody titers in seropositive participants at baseline



B) Antibody titers at baseline 105 ÷ **10**⁴ antibody 10³ 10² > 101 **AAV5** n = 36 **AAV6** n = 40 AAV8 n = 44

ed on AAV serostatus at baseline (n = 106). 95% CIs are reported for the proportions. B The edges of the boxes represent the 25th and 75th percentiles, the solid line represents the median, the circle represents the mean, and the whiskers represent the minimum and maximum titer values. A titer value of 20 was ssumed for calculations if the sample was below the level of quantification (ie, <20). Mean values as well as outlier values were potentially impacted by assumption AAV, adeno-associated virus: AAV5/6/8, AAV serotype 5/6/8; CI, confidence interva



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No seroconversio

AAV-, adeno-associated virus antibody negative: AAV+, adeno-as

Conclusions

- AAV8 at baseline

References

1. Klamroth, et al. Hum Gene Ther. 2022;33:432-41. 2. Boutin S, et al. Hum Gene Ther. 2010;21:704-12. 3. Wang L, et al. Hum Gene Ther. 2011;22:1389-401

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Seroconversion from AAV- to AAV+ was more frequently observed for AAV6 than for AAV5 and

AAV+ to AAV- seroconversions were more frequently observed for AAV5 and AAV8 than AAV6 at

Figure 4. Seroconversions at the A) 3- and B) 6-month follow-up time points

N = 20 participants with a baseline measurement were lost to follow-up and did not have a follow-up measurement. Forty-five participants had a re-test at 3 months; 41 participants have a re-test at 6 months. For seroconversions, a participant could only go from antibody negative to antibody positive if they were antibody negative at baseline and vice versa ciated virus antibody positive: AAV5/6/8, adeno-associated virus serotype 5/6/8

Consistent with previous observations,¹ AAV5 had a lower seroprevalence relative to AAV6 or

Seroconversion from AAV+ to AAV- was more frequently observed than AAV- to AAV+

- The impact of expected analytical and biological variability on test outcomes cannot be fully ruled out especially in people whose titers were close to the cut off level

 Baseline AAV titers were notably higher for AAV6 relative to AAV5 and AAV8, which may explain why individuals who were AAV6+ at baseline were less likely to seroconvert to AAV6- at follow-up Despite small sample size, data from the SAAVY study strengthens growing evidence that PwHA without AAV antibodies are likely to remain AAV- over a 6-month period

